EFFECT OF DRUG DELIVERY SYSTEM CONFIGURATION ON PERFORMANCE OF MULTI-LAYERED PELLETS

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This thesis was submitted in Partial Fulfillment of the Requirements for the Master Degree in Pharmaceutical Sciences

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May, 2011

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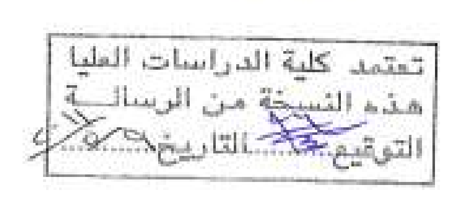
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عنوان الرسالة:

EFFECT OF DRUG DELIVERY SYSTEM CONFIGURATION ON PERFORMANCE OF MULTI-LAYERED PELLETS

اعلن بأنني قد التزمت بقوانين الجامعة الأردنية وأنظمتها وتعليماتها وقراراتها السارية المفعول المتعلقة باعداد رسائل الماجستير عندما قمت شخصيا" باعداد رسالتي وذلك بما ينسجم مع الأمانة العلمية وكافة المعايير الأخلاقية المتعارف عليها في كتابة الرسائل العلمية. كما أنني أعلن بأن رسالتي هذه غير منقولة أو مستلة من رسائل أو كتب أو أبحاث أو أي منشورات علمية تم نشرها أو تخزينها في أي وسيلة اعلامية، وتأسيسا" على ما تقدم فانني أتحمل المسؤولية بأنواعها كافة فيما لو تبين غير ذلك بما فيه حق مجلس العمداء في الجامعة الأردنية بالغاء قرار منحي الدرجة العلمية التي حصلت عليها وسحب شهادة التخرج مني بعد صدورها دون أن يكون لي أي حق في التظلم أو الاعتراض أو الطعن بأي صورة كانت في القرار الصادر عن مجلس العمداء بهذا الصدد.

توقيع الطالب: التاريخ: ٥ / ٥ / ٢٠١١م



EFFECT OF DRUG DELIVERY SYSTEM CONFIGURATION ON PERFORMANCE OF MULTI-LAYERED PELLETS

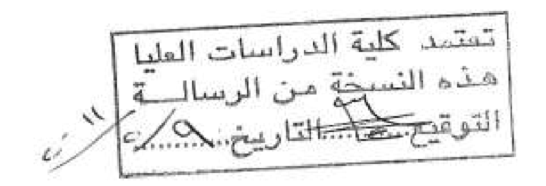
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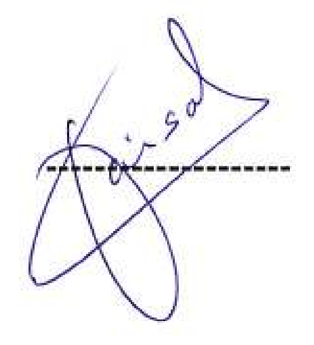
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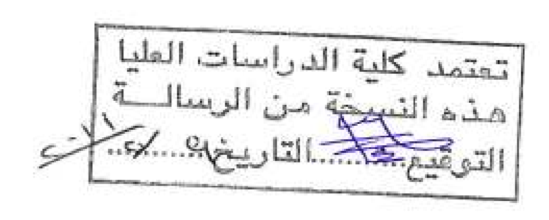


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Dedication

To my mother, who taught me that the best kind of knowledge is that which is learned for its own sake.

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First of all, I express my heartfelt gratitude to my most respected supervisor,

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Whose extreme generosity in assistance and support will be remembered always

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To all of the above, I extend my deepest appreciation.

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LIST OF ABBREVIATIONS

NUMBER	Symbol/Abbreviation	Definition
1	B.P	British Pharmacopoeia.
2	µm	Micrometer.
3	ml	Milliliter.
4	RH	Relative Humidity.
5	F_2	Similarity factor.
6	F_1	Difference factor
7	Tg	Glass transition
9	SLS	Sodium Lauryl Sulfate.
10	HCl	Hydrochloric acid.
11	MFT	Minimum film forming temperature
12	°C	Celsius degree
13	TWG	Total weight gain

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ABSTRACT

The purpose of this study was to develop caffeine sustained-release beads were prepared by the pelletization technique.

Controlled release caffeine beads were prepared by loading the caffeine on inert beads followed by coating with different functional polymeric films with aqueous dispersion coating mixtures such as Eudragit® E_{100}have been employed as a protective polymer and films of different solubility characteristics can be produced ammonio methacrylate copolymer (Eudragit RL 30 D) and ammonio methacrylate copolymer (Eudragit RS 30 D) as a controlled or sustain release polymers were used at a ratio of 30:70 in Fluid Bed Coater (Wurster Column).

Thickness of coating, duration of curing or accelerated stability condition and process condition of fluid bed coater such as temperature, and air flow were affect on the release of caffeine from coated beads for 8 hour.

Caffeine coated beads were subjected for dissolution at (0.1 N) HCL for 2 hours and PH 6.8 for 6 hours to evaluated in vitro caffeine release profile from coated beads. Caffeine coated beads were stored in an oven at 50 °C and accelerated stability condition at 40 °C / 75 % RH. In all cases the rate of release of caffeine was decreased from the coated beads.

In conclusion, pelletization technology has revolutionized the pharmaceutical research with its wide range of applications which includes immediate and sustained release oral, parenteral, subcutaneous products.

1. INTRODUCTION

1. 1. Need for Controlled Drug Delivery systems:-

Pharmaceutical dosage forms (e.g., tablets, capsules) are frequently coated with polymeric films for various reasons, such as, to facilitate swallowing, to protect the drug during storage against moisture or oxygen, to protect the stomach from the drug, or to control the drug release kinetics. If the drug is administered using a traditional immediate release dosage form (e.g., tablet) the entire dose may be rapidly dissolved within the stomach. On absorption into the blood stream a high maximum plasma concentration (peak) results, with the risk of toxic side effects for drugs with a narrow therapeutic window. To overcome these problems, the time course of drug release from the dosage form can be controlled, using for instance polymeric drug delivery systems. Controlled or sustained release of drug application within the pharmaceutical industry require consistent smooth surface with a narrow size distribution, to ensure uniform coating and accurate free flow of granules for filling operations like capsule filling (Woodruff and Nuselle, et al., 1972). Oral administration is preferred route of drug administration for most therapeutic agents (Banker, et al., 1986). In addition, much effort has been directed in developing modified release oral dosage forms allowing for better control of drug therapy (Rane, et al., 2010).The controlled oral drug delivery systems, has received major interest because of its greater popularity as drug delivery (Banakar, 1987; Khan, et al., 1994; Sastry, et al., 1997).

As a result, various controlled drug delivery are currently available for patient use (Grass and Robinson, 1990). The main advantage of controlled dosage forms is patient compliance compared with conventional formulations to achieve the same therapeutic effect. The patient's compliance can be improved by reducing the number of dose administrations (Rowland, et al., 1999).The drug in controlled delivery system is achieved via monolithic (matrix) devices in such which the active agent is dispersed within the polymer matrix, or compressed of a polymer/drug mixture by dissolution or melting. The dosage release properties may be dependent upon the

solubility of the drug in the polymer matrix (Singh,et al., 1968) the drug release is controlled by diffusion through the matrix, swelling of the matrix and /or erosion (Siepmann, 2001).Or reservoir devices a typical approach to controlled release is to encapsulate the drug entirely e.g., as a core within a polymer film (Kala ,et al., 1979), or can be surrounded by a membrane film barrier which controls the release rate of drug. This is important when potent drugs with a low therapeutic window are used in order to ensure drug levels below the minimum toxic and above minimum effective concentration.

Different physicochemical processes may be involved in the control of the resulting drug release rate, e.g., dissolution, diffusion, crack formation within the polymeric shell (coating), osmotic effects and polymer swelling (Siepmann,et al., 2001) for the preferred oral route of administration, water-insoluble film coatings are frequently used to control drug release within the gastro-intestinal tract. Common water insoluble polymers are either synthetic acrylate derivatives, such as poly (ethylacrylate-comethyl methacrylate-co-trimethylammonioethyl methacrylate chloride) and poly (ethylacrylate-co-methyl methacrylate) (McGinity, 1997) or ethylcellulose (a partial ether of the biomacromolecule cellulose) which is a good film former and generally regarded as nontoxic, non allergenic and nonirritant (Wade, et al., 1994) if pharmaceutical dosage forms are surrounded by a continuous polymers coating film, the resulting drug release rates may be too low to allow sufficient drug release within the gastro-intestinal transit time. This provides the plasma drug concentrations at steady state over a prolonged period of time. (Chiao and Robinson, 1995). At a zero-order rate is possible by controlled release systems. It is essential to achieve regular plasma drug concentrations for absorption, and allows for maintenance of drug concentrations within a therapeutic effect. As shown in figure 1.

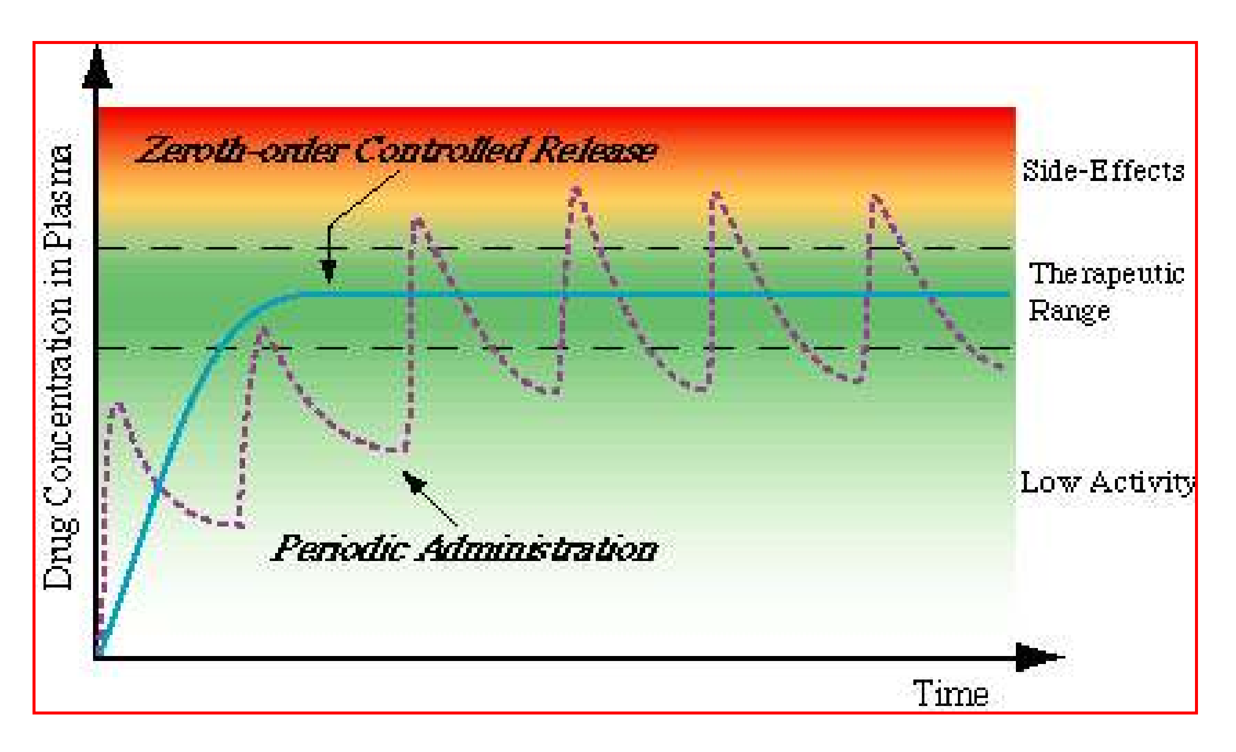


Figure 1.Schematic Representation of controlled release W.H. Helfand and D.L.Cowen, **Evolution of Pharmaceutical Oral Dosage (1983).**

1.2.Classification of Controlled Drug Delivery Systems:-

The term "sustained release has been constantly used to describe the pharmaceutical dosage forms formulated to retard or delay the release of a therapeutic agent or selective delivery of the drug to the target organs of body, and the duration of action of drug is sustained .The term "controlled Release" is one which delivers the drug is predetermined rate, locally or systemically for a specified period of time to its site of action (Chien Y. W, 1982).Base on their technical sophistication alternate drug delivery system can be classified into:-

I. Activation-modulated drug delivery systems.

II. Rate-preprogrammed drug delivery systems.

III. Feedback regulated drug delivery systems.

I-Activation-modulated drug delivery Systems:-

The energy supplied externally is activation process in controlled release the drug delivery system is activated by physical, chemical or biological process include PH controlled, mechanical activation, and magnetic activation, Osmotic pressure, ion-activated, hydrolysis activated, enzyme activated, vapor pressure. (Theeuwes, 1983).

II-Rate-preprogrammed drug delivery Systems:-

The controlled release the drug delivery system in a preprogrammed rate. By monolithic (polymer matrix) devices by diffusion controlled drug release, the drug reservoir is prepared by uniformity dispersing drug molecule in a rate-controlling polymer matrix fabricated from polymers e.g. NitroDur - Designed for application onto intact skin for 24 hrs to provide continues transdermal infusion of nitroglycerine (Keith ,1983) In micro reservoir controlled drug delivery systems, the drug reservoir is fabricated by micro dispersion of an aqueous drug suspension by a high-energy dispersion technique in a biocompatible polymer e.g. Nitrodisc system – Engineered to deliver transdermal administration of nitroglycerine. Syncromate implant –Engineered to deliver subdermal administration of norgestomet. (Karim,1983).The drug reservoir such as solid, saturated suspension, or solution form by polymer film membrane permeation-controlled drug delivery systems, the dosage forms release controlling by polymeric film membrane permeability Norplant sub-dermal implants e.g. An implant designed to release levonorgesterol continuously for seven days (Weiner, 1979).

III- Feedback regulated drug delivery systems:-

The release of the drug molecules from the delivery system is activated by a triggering agent such as biochemical substances in the body and also regulated by its concentration via some

feedback mechanism e.g. Bio-erosion regulated hydrocortisone dispersion.(Helier and Trescony , 1979).

1.3. Eudragit RS, RL, E® 100 and their application in active layering:-

Poly methacrylates are primarily used in oral formulations as film coating agents (Lehmann 1973; Lehmann 1981; Okor 1990). Depending on the type of polymer used, films of different solubility characteristics can be produced. Eudragit RL 30 D and Eudragit RS 30 D are aqueous dispersion of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups (Kibbe, 2000; Lehmann 1996; RohmGmbH & Co., 2005). Eudragit RL 30 D is ammonio methacrylate copolymer and Eudragit RS 30 D is ammonio methacrylate copolymer polymer.

The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers (Lehmann, 1996; Rohm GmbH & Co., 2005). Films prepared from Eudragit RL 30 D are readily permeable to water and to dissolve active substances, whereas films prepared from Eudragit RS 30 D are less permeable to water (Lehmann, 1996; Lehmann, et al., 2001). Film coatings prepared from both polymers give pH-independent release of active substance. The most widely used aqueous polymer dispersions for sustained-release coating applications by combining different polymethacrylate coatings it is possible to adjust drug release profiles. EUDRAGIT® E 100 polymers used in seal sensitive actives and increase patient compliance by taste and odor masking. EUDRAGIT® E100 provide the desired effect, making it an extremely economical application. The advantage of protective EUDRAGIT®E100 coatings: pH-dependent drug release, protection of sensitive actives, taste and odor masking, moisture protection, Economical application, improved transit of the dosage form and smooth and glossy surfaces, excellent coating (Evonik Industries, Pharma Polymers, 2008).

2. Multiparticulate Beads System:-

Multiparticulates, (micro pellets, pellets, Minitablets and granules) significantly gained in importance in the pharmaceutical industry (Fukumori, et al., 1997) The recent interest in multiple-unit dosage forms is a result of the advantages they offer over the single-unit systems (Follonier and Doelker, 1992; Vial-Bernasconi et al., 1988). Multiparticulate offer several advantages compared to conventional single unit dosage forms. Multiple-unit forms offer more predictable gastric emptying, less dependent on the state of nutrition, a high degree of dispersion in the digestive tract, less absorption variability, and a lesser risk of dose dumping. The multiple-unit forms are also more suitable for formulations with acid-sensitive drugs (Feilden, et al. ,1992).They are also better distributed and less likely to cause local irritation (Tang, et al., 2005) and local concentration of drug is minimized due to the greater extent of dispersion of beads (Haigh, 1985; Eskilson, 1986). The extrusion spheronization technology may be used to produce extended release multiparticulates in a multistage using a carrier polymer similar to the matrix concept (Breitenbach, 2002) , Pan coating (Ghosh, et al., 1999) and fluid bed coating (Singh, et al., 1995, 1996) have been employed for membrane type controlled release

The basis of manufacturing of multiparticulate for extended release formulations by substrate (inert beads) such as Nonpareil containing drug with the active excipient is dissolved or suspended in appropriate polymers solvent for adhesion and can be layered onto the core beads The drug layering can be protected from controlled release coating by applying a seal coating (if required) and barrier film membrane in topcoat to reduce electrostatic and protect functional membrane (Porter, et,al., 2010).

Starter inert beads such as sugar spheres (e. g.SureSpheres®), micro crystalline cellulose spheres, silica beads, or others that are used for drug layering. Sugar spheres are widely used in formulations due to their acceptability and availability in various size ranges. The important aspect during drug layering is to achieve a uniform drug layer to ensure content uniformity

(Rege, et al., 2005).The release mechanisms of the drug from coated beads according to the structural arrangement of the individual function polymer and the active agent is incorporated in the polymer or excipient in dispersed or dissolved form. The changes in size between the inert beads drug layering is undesirable in coating process may influence surface area available for drug layering and coating and thus affect drug release rate. This has been attributed to a decreased film thickness of the barrier membrane coat arising due to increased surface area with the smaller sized pellets. (Rege ,et al., 2005), this problem can be overcome by the drug layering to be protected through applying a seal coating may be applied to the starter core or drug containing pellets to:-

(I) Improve the hardness of the friable starter core or drug layered pellets.

(II) Separate the drug from the core or the barrier membrane, if Incompatible.

(III) Provide a smooth surface on drug-loaded pellets for further functional coat.

(IV) Reduce or control the influence of osmotic pressure exerted by sugar (starter core) on drug release (Porter et, al., 2011).

Release of drug from such multi-particulate beads is an affected by the shape of the individual beads and available surface area for reaction shows a comparison of drug release using starter seeds with smooth versus rough surfaces drug layered and barrier membrane coated. The release from a smooth core was found to be slower than the rough core this has been attributed to a uniform drug layer and barrier membrane coat on the smooth core as compared to the rough surface core. The roughness may have created weak coating that lead to increased drug release rates (Rege, et al., 2005).

2.1. Pellets as solid dosage form:-

The “Pellet” is agglomerates of fine powders or granules of bulk drugs and excipients. small, free-flowing, spherical or semi-spherical solid units with a narrow size distribution, typically from about (0.5 mm to 1.5 mm,) and are intended usually for oral administration (Elchidana, et al., 1999;Ramarao, et al, 1998), varying between (500 -1500 μm) for pharmaceutical applications (Ghebre-Sellassie and Knoch, et al., 2002), Coated pellets are frequently used for oral controlled drug delivery (Ozturk, , et al.,1990; Fukumori, 1997; Ghebre-Sellassie,1997 ,McGinity, 1997, Sadeghi, et al.,2000) compared to coated tablets and capsules. Pellets are a great interest to the pharmaceutical industry for a variety of reasons. (Ahmed and Karsten, et al., 2007) spherical particles are not only offer flow but offer high degree of flexibility in the design and development of oral dosage form like suspension, sachet, tablet and capsule shown. They offer significant therapeutic advantages over single unit dosage forms (Conine, et al., 1970) the technological advantages of spherical particles include the following:-

i. In case of oral products administration micro pellets solve problems taste-masking and unpleasant odors (Fumio, et al., 2004).
ii. They can also be used to provide different release profile at the same or different sites in the gastrointestinal tract.
iii. Coating of drug pellets with different polymers to achieve controlled release rate of drugs.
iv. For immediate release products larger surface area of pellets enables better distribution, dissolution and absorption (Dokoumetzidis, et al., 2006).
v. Chemically incompatible products can be formulated into pellets and delivered in a single dosage form by encapsulating them (Shell, et al, 1999; David et al, 2007).
vi. Pellets also reduce variations, thus, intra- and inter subject variability of plasma profiles
vii. Spherical particles exhibiting excellent flow properties and these are characterized by a smooth surface free of dust and thus provide optimal conditions for subsequent film coating (Viness, et

al., 1999).The pellet type of sustained-release preparation is often referred to as bead-type preparation. In general the beads are prepared by coating drug onto perforated cores called nonpareil seeds. They may be further coated with a protective coating to allow a sustained or extended release of the drug (Shargel and Andrew, et al., 1941). There are several manufacturing techniques for production of spherical beads. Newer equipment like centrifugal fluid bed granulators have also been used for production spherical pellets the most widely used pelletization processes in the pharmaceutical industry are extrusion/spheronization, solution/suspension layering, powder layering and direct pelletization. (Porter, et al., 2010).

2.2. Coated pellets for controlled drug release:-

2.2.1. Mechanism of release from coated pellet

Drug release from coated pellets coated with polymeric film widely accepted for use as a sustained release coating for pharmaceuticals formulation, the release rate was studied as a function of coating thickness and plasticizer content, in the dissolution medium, pellet is often related to undulations of the drug layer underneath, and weight-gain does not reflect this information (Heinicken and Schwartz, et al., 2007) on drug release using in vitro release dissolution (Shao, et al., 2002; Muschert, et al.,2009; Dashevsky, et al ,2005; Siepmann et al , 2008, 2007).There are several possible mechanisms by which release from multiparticulate dosage forms coated with water insoluble polymers may occur (T.K. Sherwood, et al., 1975).

i. Diffusion / dissolution controlled delivery system.

ii. Polymer erosion controlled drug delivery system.

iii. Osmotic pressure controlled drug delivery System.

2.2.1.1. Diffusion / dissolution controlled delivery system:-

The oral controlled release dosage from are based on diffusion when contact with aqueous fluids of the gastrointestinal tract, fluid will enter the drug particle by diffusion. Dissolution of the drug will occur and drug molecules diffuse from a region of higher concentration to lower concentration until equilibrium. The rate of drug release which depended nature of the drug, the coating thickness, function of polymer (sustain or immediate release) and addition of plasticizer level as will the use of dissolution rate modifiers. By using these techniques, the structure of the film can be altered (Cole, et al., 1995; Lippold, et al., 1999), instead of diffusing through the polymer, pores are created due to dissolution of parts of membrane the drug can be diffuse through channels or pore within the membrane, thus facilitating the release rate of drug (Singh, et al., 1968).

2.2.1.2. Polymer erosion controlled drug delivery system:-

This technique has been used where multipartculate systems were coated with simple fatty materials such as beeswax or glyceryl monostearate. In erosion-controlled systems, the drug is dispersed uniformity in the hydrophilic polymer matrix. When contact with the aqueous fluids of the gastrointestinal tract, these systems swell by polymer and drug dissolution. The diffusion of the drug in the gel layer formed is slower than the polymer dissolution rate or erosion of the gel (Lee, et al., 1985; Ford, et al., 1987), in the erodible hydrophilic matrix, the controlled drug release can be either by erosion in the case of poorly soluble drugs or by diffusion of the drug through the gel layer and erosion of the gel in the case of highly water soluble drugs (Ford, et al.1985a, 1985b, 1987; Lee, et al., 1985).

2.2.1.3. Osmotic Pressure controlled drug delivery System:-

Osmotic effects can be control of drug release from coated pellets, as well as known an osmotic active core beads surrounded by a semi permeable polymer membrane. Any way an osmotic gradient is created across the polymer film (Schmidt, et al., 2000).

Osmotically driven release depends on the porosity of the polymeric membrane and the osmotic pressure of core and the drug (Ozturk, et al., 1990).By movement of solvent from lower to higher concentration water enter into the system as soon as the coated pellet when contact with the aqueous environment and the saturated drug solution exist only through pores in outer membrane.

3. Principle of fluid bed coating process:-

3.1. Film coating Strategies:-

With aqueous dispersions, the process conditions such as spraying rate, drying temperature, and spraying pressure must be carefully chosen because if, as a result of processing conditions, the product bed temperatures are too low, they will be insufficient to achieve the desired filming above minimum film-forming temperature. The product temperature during coating should be approximately 20°C above the minimum film formation temperature in order for good film formation to occur (Dashevsky, et al., 2005). On the other hand, excessively high product bed temperatures allow the dispersion agent to evaporate so rapidly that the film former is spray dried (Thoma and Bechtold, 1999).

3.2. Film coating equipment:-

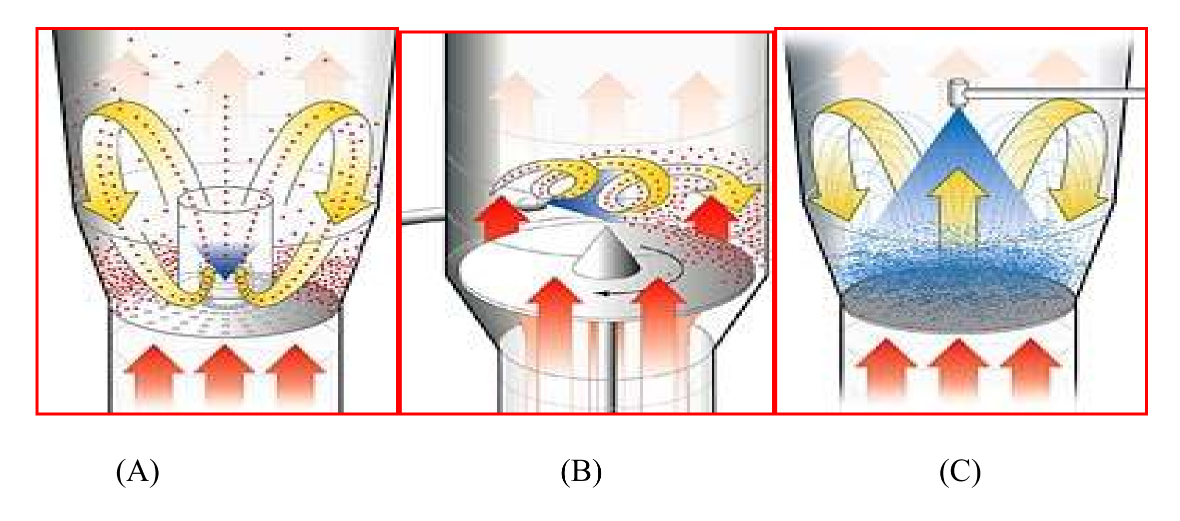
The coating of multi-particulates was used to produce prolonged or extended release formulation is becoming mostly popular by using in fluidized-bed coating (R.Wiwattanapatapee, 2004). The beads are coated in fluid bed equipment and atomized coating material is sprayed through nozzle

form the top, the side or the bottom into fluidizes bed, The selection correct and balance parameters of coated pellet such as temperature and speed agitation of beads, air flow, polymeric content formulation and drying time during the coating processes may be affect on film formation by produce irregular, cracking, crushing and thin film coatings. Several techniques can be used in fluidized bed coatings or dryer in different batch sizes of core materials. With top spray coating in the fluid bed (batch and continuous), particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate. The coating liquid is sprayed into the fluid bed from above against the air flow (countercurrent) by means of a nozzle this process is used for general in to enteric coating. (Glatt. Fluid Bed Coating. Technologies 2004-2008, www.glatt pharmaceutical.com)

In the Wurster process, a complete sealing of the surface can be achieved with a low usage of coating substance. The spray nozzle is fitted in the base plate resulting in a spray pattern that is concurrent with the air feed. By using a Wurster cylinder and a base plate with different perforations, the particles to be coated are accelerated inside the Wurster tube and fed through the spray cone concurrently. This process is suitable for a controlled release of dosage from (Glatt. Fluid Bed Coating. Technologies 2004-2008, www.glatt pharmaceutical.com)

In Tangential spray coating (Rotor pellet coating) used for coatings with high solid content. The bead is move into a spiral motion by a rotating base plate, which has air flow fed into the pellets at its edge. The spray nozzle is arranged tangentially to the rotor disc and also sprays simultaneously into the pellets, very thick film layers can be produce from rotor method (Glatt. Fluid Bed Coating. Technologies 2004-2008, www.glatt pharmaceutical.com) there are three basic configurations in fluidized bed processing: -

These configurations are used for coating or drying in laboratory and commercial scale equipment shown in Figure 2.



(A) (B) (C)

Figure 2: Schematic Figure of a fluidized bed apparatus: (A) bottom sprays with Wurster column insert; (B) tangential spray technique (C) Top spray technique; **(Felton, 2007)**

The coatings involved use various polymers function with controlled release profile by using different water solubility or permeability many processes have in common essential coating beads steps:-

(i) The droplet formation from the coating formulation by the spray nozzle, (ii) contact and adhesion of the droplets onto the beads surface (iii) spreading and coalescence around surface of beads shown as Figure 3. Film formation from aqueous dispersions is more complex (Fukumori, et al, 1997). Several theories to explain the formation of a continuous polymeric film from discrete polymer particles have been presented (Dillon, 1951; Nagakami, et al., 1991). Upon water evaporation during the coating process the polymer particles get into contact with each other and form a layer of closed packed polymer spheres with water filled cavities (Onions, 1986). Polymers are pulled closer together as water further evaporates due to surface tension (Wheatley, 1997). Finally, particle coalescence occurs when the capillary forces are sufficiently strong (Paeratakul, 1993). Shown as Figure 4

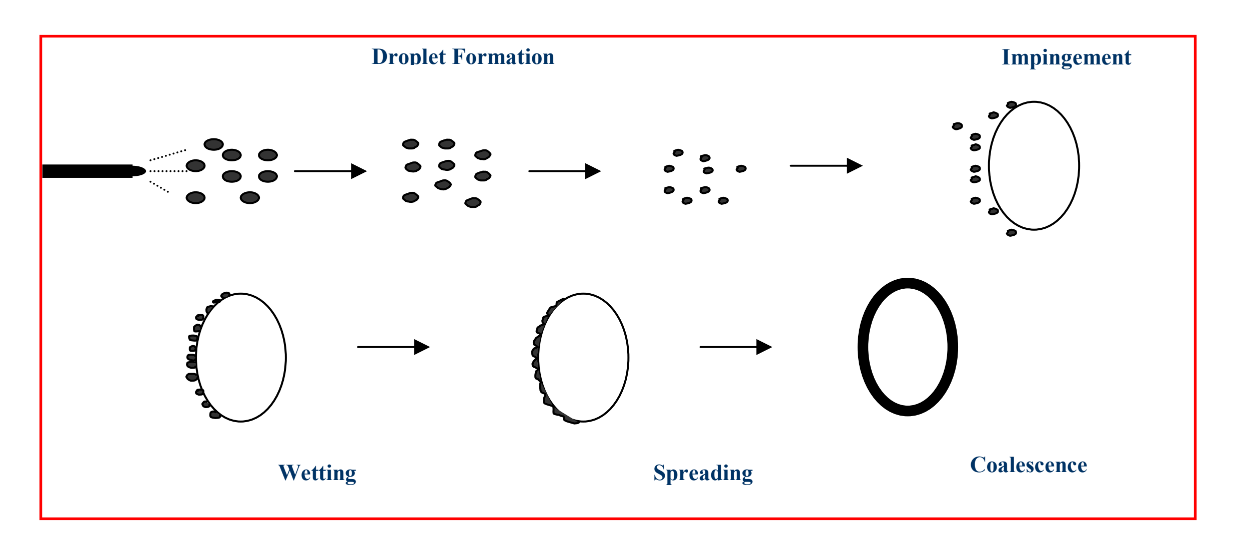


Figure 3. Schematic presentation of the film forming mechanism from aqueous polymer dispersions Pharmaceutical Film Coating Technology **(BAPA Annual Convention, 2009)**.

Polymeric formulation can be applied from dry powder, aqueous dispersions and granules in different solubility or permeability include ethyl cellulose and modified acryl ate derivatives, the application of organic polymer solutions has been historically used for film coatings. Toxicity and environmental concerns associated with the use of organic solvents have pushed the pharmaceutical industry to explore alternative procedures. Many polymers have been formulated into aqueous colloidal polymer dispersions or aqueous micronized polymer dispersions (K. O. R. Lehman, 1997; U. Iyer, 1990; T. A. Wheatley and C. R Steuernagel, 1997). Aqueous coatings are unsuitable. A high energy of evaporation of water requires a higher coating temperature and/or long processing drug migration into the coating could occur during aqueous-based coating, depending on the drug molecule (Ghebre-Sellassie, 1987) to overcome these problems of liquid-based coatings, a novel alternative coating technology based on polymer powder has been introduced the dry powder coating (S.Obara, et al., 1999), offered much shorter processing time. Thus, this new technique offers a new possibility of a coating system for extended-release dosage forms. process parameters and coating composition play an important role in coating of pellet, it would be necessary to optimize the parameters to success of coating process:-

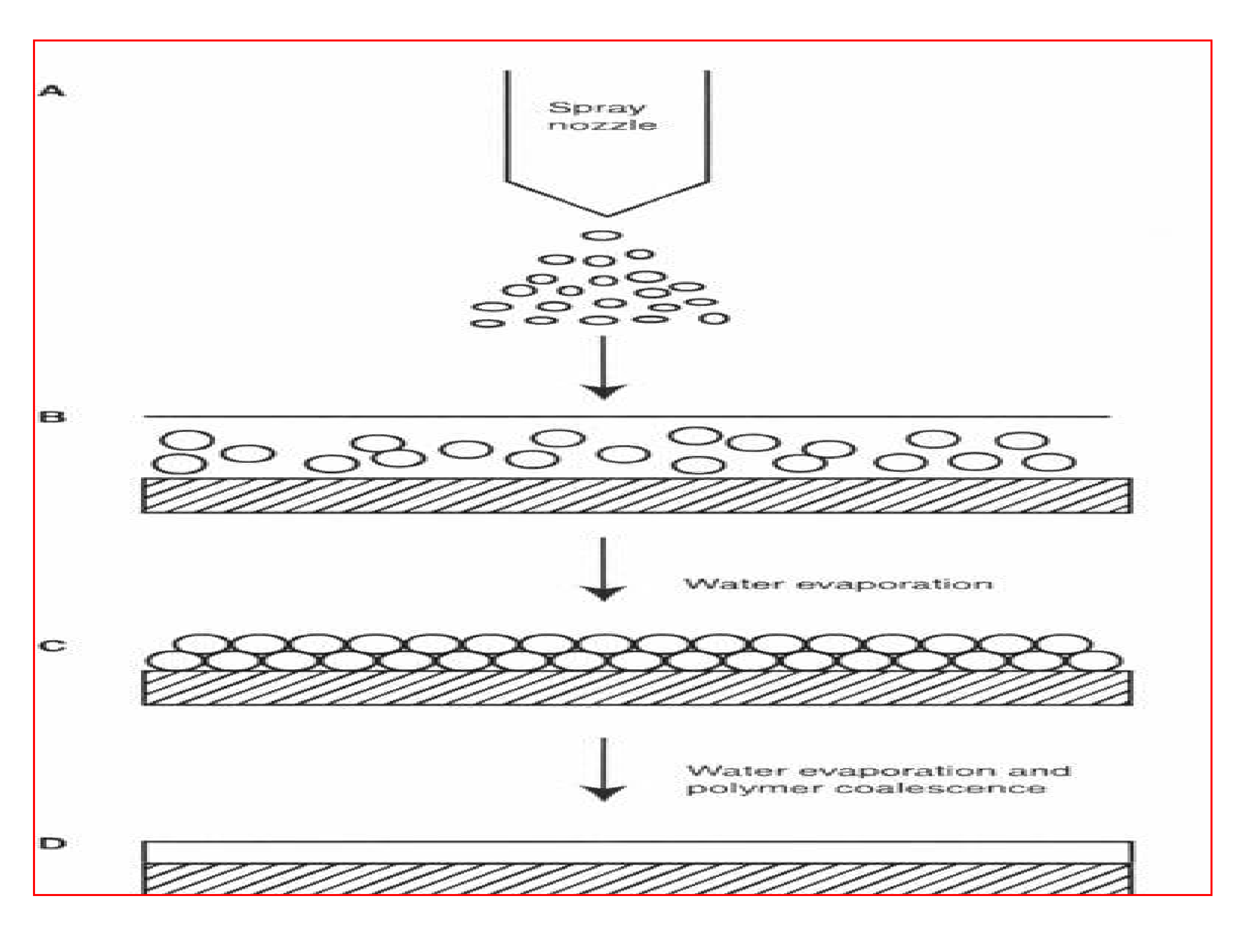


Figure 4. Schematic representation of the film formation process for and aqueous polymeric dispersion: (A) atomization of polymeric dispersion; (B) deposition of the polymeric dispersion on the substrate surface; (C) packing of the polymer spheres with water filling the void spaces; (D) formation of continuous polymeric film **(Felton, 2007).**

3.2.1 Inlet air temperature:-

The inlet air temperature affects the drying efficiency and the uniformity of coatings (Twitchell, et al., 1995a). High inlet air temperature increases the drying efficiency of the aqueous film coating process and a decrease in the water penetration into the core or decreases the core porosity, tensile strength and residual moisture content of coatings (Twitchell ,et al ,1995a; Poukavoos,et al.,1994) high air temperature increases the premature drying of the spray during coating process and, subsequently, decreases the coating efficiency (Porter, et al.,1997; Rege ,et al., 2002).

3.2.2. Spray rate:-

The spray rate is an essential parameter since it affects the moisture content of the formed coating film and, subsequently, the quality and uniformity of the film (Obara, et al 1995; Franz, et al, 1983; Porter, et al., 1997) A low coating liquid spray rate causes incomplete coalescence of polymer components due to insufficient wetting, which could effect in brittle films. (Obara, et al., 1995). A high coating liquid spray rate may result in over wetting of the bead surface and subsequent problems such as picking and sticking .(Obara,et al.,1995 ;Franz ,et al.,1983) If the spray rate is high and the pellet surface temperature is low, films are not formed during the spraying but the post drying phase, and rapid drying often produces cracks in the films .(Obara , ,et al,.1995).

3.2.3. Atomizing air pressure:-

In general, increasing the spraying air pressure decreases the surface roughness of coated beads and produces denser and thinner coated films (Twitchell,et al., 1995a ;Twitchell,et al,. 1995b ; Tobiska ,et al ,2003) .If spraying air flow is inappropriate , the film thickness variation are greater due to change in the film density and spray loss. In addition, with low spraying air pressure cause over wetting the beads surface are sticks to each other.

4. Characterization of pellets:-

In order to meet the requirements of size distribution, shape, surface roughness, Density and friability, including the reproducibility of morphologic properties of the pellets, pellets have to be tested:-

4.1. Size distribution:-

The size distribution of pellets should be as narrow as possible because it will ensure a minimum variation in coating thickness and coating performance within the batch. If the pellets are intended for compression, wide size distribution may lead to segregation and variations in content uniformity. The size of the pellets also affects compaction properties and drug release from the compacted pellets. At the same coating level, smaller pellets were more fragile than larger pellets. This is due to the reason that increased surface area resulted in reduced film thickness (Flament M-P,et al,. 1994) It was also found that increase in particle size resulted in more damage to the coating, as indicated by larger difference between the release profile of tablets and uncompressed pellets.

4.2. Shape and surface roughness:-

In order to obtain good performance of coated pellets it is necessary to have spherical and Smooth particles suitable for subsequent coating, usually for achieving modified-release. The commonly used method is the analysis of microscopic or non-microscopic pictures of interest. Scanning electron microscopy (SEM) is a technique of choice for measuring the shape and surface smoothness of the pellets to support visually the other qualitative and quantitative results (Costa et al., 2004). Shape of the pellets was found to affect the compression behavior and tablet forming ability of granular materials. More irregular shape induced more complex compression behavior of granules i.e., more attrition of the granules was induced and increased deformation was resulted (V.S.N.Murthy Dwibhasyam, 2008) Isometric shaped pellets offer less contact points and uniform drug release when compared with an isometric shaped particles.

4.3. Porosity:-

Increased pellet porosity increased the degree of deformation of pellets during compression and tensile strength of tablets because of formation of stronger inter-granular bonds. The effect of intra granular porosity on drug release is also high. Compacted pellets of high porosity were densely packed and deformed. So the drug release was unaffected. The drug release was markedly increased when low porosity pellets were compacted due to slight densification and deformation. So the use of highly porous pellets was advantageous, in terms of preserving the drug release profile after compaction, compared with pellets of low porosity. (Tuton A, et al., 2003). Porosity of pellets depends upon materials such as granulating fluid used in their formation. Increasing the amount of water in the mixture resulted in harder and less porous tablets and a slower drug release. Pellets prepared using 95% ethanol had excellent compressibility compared with that of water (Bodmeier R, 1997). The final porosity attained after compaction depends on pressure applied. Unlubricated pellets require higher pressures than lubricated. (Bodmeier R, 1997).

4.4. Density of pellets:-

Variation of density of pellets from batch to batch affects the potency of finished capsules, Produces segregation during mixing and causes problems in batch size determination during coating. Bulk and tap density of pellets is measured using automated tapper, by measuring the volume of a known mass into a graduated cylinder, and is influenced by the diameter and size distribution of pellets. They are indicative of the packing properties of particles Density of pellet is required to achieve prolonged gastric residence. The critical density to achieve prolonged gastric residence may lie between 2.4 to 2.8g/cm (Bodmeier R, 1997; V.S.N.Murthy Dwibhasyam, 2008). Density and size of the pellets play an important role for achieving content

and weight uniformity. Segregation may occur when pellets are compressed using excipients with smaller particle size and density. (Bechard SR, et al., 1992).

5. Factors affecting coating Quality:-

Thickness coat and plasticizer level are important factor in coating process in controlled kinetics release. Several factors can significantly affect the drug release profiles from coated pellets.

5. 1. Drug-excipient aqueous solubility:-

The spray rate can be increased gradually. If the core is sensitive to water or moisture, (Bauer, et al., 1998), the solubility of the active ingredients may lead to migration of drug from layer to layer coating during process. This problem can be overcome by atomizing the polymer solution slowly in very thin layers and second. Preheating the core beads at 40 to 45° C before starting coating process.

5.2. Coating level (coating thickness):-

The coating thickness of pellets is described by the permeability of the drug from the core to medium through barrier membrane film is depended on the percentage solid weight gain in coating dispersion deposition on the core beads during coating process. Generally an increase in coating thickness meaning weight gain increases Therefore, the rate of drug release is inversely proportional to diffusion path length. (Thickness coat) .So, increasing the film thickness (or weight gain) would reduce the drug release rate by increasing diffusion path length. Coating thickness may also influence the release drug profiles. If the film is thin, fast drug release profile may be recognized the drug is the diffusion path across the core is limiting with time, if the thickness of coating membrane will be the rate-limiting factor and drug release will follow nearly a zero-order release (Zhang, et al., 1991).

5.3. Curing conditions (thermal treatment):-

Film formation is it is not complete coalescence during coating process time. Under curing condition in an oven at a specific temperature and period of time is very important point in coating technology where the coated dosage forms are stored at temperature for short period. Curing of coated beads after coating process is a significant influence on the drug release profile and mechanism of drug release (Bodmeier and Paeratakul, 1994). The effect of curing on drug release is depended upon the physiochemical properties of the drug, polymer involved in the coating solution, temperature and duration of curing condition. Both decrease and increase in drug release profile have been observed to varying degrees (Bauer, et al., 1997).

5.4. Substrate (core):-

The size and shape of core beads may influence on controlled drug delivery system in coating process however. larger core beads tend to be less fluidized process in equipment compared to smaller core beads (Wesdyk, et al., 1993), leading differences in coating thickness may influence surface area available for drug layering and coating and thus affect drug release rate (Rege et al., 2005). Smooth surface of core beads tends to a uniform drug layer and barrier membrane coat compared to the rough surface of beads during coating process towards film formation mechanism on surface core beads.

5.5. Drying temperature:-

The film formation of aqueous latex film techniques is a influence of minimum film forming temperature (MFT) (Lippold, et al,1990; Lehman and McGinity,1997).In general the drying temperature should be exceed the minimum film forming temperature (MFT) by 10 degree C to 20 degree C. the importance of the MFT on the bed temperature of a coating process film formation is affect on the polymeric dispersions coalescent mechanism for film formation will

have a low glass transition temperature coalescence of polymeric particles that result coalescence film occurs only above the MFT.

5.6. Solids Content:-

Uniformity film formation is more when the total solids content is reduced. However very low solid content may lead to increase in duration of coating process. (Bindschaedler, et al., 1983).

6. Coating systems:-

6.1. Film coating formulations usually contain the following components

A typical film coating system consists of three main ingredients:-

I- Polymer compound

II- Plasticizer

III-Active excipient

6.1.1. Polymer compound:-

The polymer used in preparation of coated pellet plays an important role in drug release profiles it must have sufficient flexible or elasticity properties to prevent crack or crushing of coating polymer or to prevent the changes in shape and deformation during coating. For example polymers used in film coating are cellulose derivatives or acrylic polymers and copolymers. (Nyamweya, et al, 2001; Hogan, 1998).

Ethyl cellulose polymer is weak mechanical properties and hence the beads coated with ethyl cellulose showed loss of sustained or prolonged release properties. For use of pseudo latexes plasticized ethyl cellulose showed minimal effect on mechanical properties of ethyl cellulose making it brittle with low values of strength and elongation. Crystals, granules or pellets coated with aqueous acrylic polymer dispersions (Eudragit NE 30D, Eudragit RS/RL 30D) were more

flexible or elasticity than ethyl cellulose films and they can be compressed with little damage to the coating. (Bodmeier, 1997).

6.1.2. Plasticizers:-

Effective plasticization is critical point when using polymeric dispersions to ensure sufficient free volume to facilitate coalescence them .plasticizers are relatively low molecular weight materials which have the ability to change the physical properties of the polymer to render it more useful in performing its function as a film-coating material. (Hogan, et al, 1998; Rowe, et al., 2005) Since plasticizer is essential for mobility of the macromolecules, the type of plasticizer might affect the degree of polymer particle coalescence in the film coatings and/or the release profile. In an attempt to alter the film formation, the water-insoluble plasticizer dibutyl sebacate (DBS) was used instead of the water-soluble plasticizer triethyl citrate (TEC). The decrease in the relative drug release rate upon 3 and 6 months storage under stress conditions were even more pronounced than in the case of the water-soluble plasticizer TEC Plasticizers are classifying in three groups. Polyos type contains glycerol, propylene glycol, PEG (Polyethylene glycol). Organic esters contain phthalate esters, dibutyl sebacete, citrate esters, and triacetin. Oils /glycerides contain castor oil, acetylated, monoglycerides, and fractionated coconut oil.

6.1.3. Active Excipient:-

Active excipient is an essential in coating process by enhance contact or adhesion and increase deposition quantity of polymer on core beads for example, talc (mean particle size 17.4 m) was use a glidant for the polymer powder to improve the powder flow into the spraying chamber and also as an anti-tacking agent during the coating process.

7. Related studies:-

Recently, many of research effort have been directed toward preparing coated pellet by multilayer coated and studying the effect of optimization parameters or formulation on drug dissolution performance of them.

For example (Wei He, et al., 2009), investigated the effect of multi-layer film coatings on omeprazole. The system consists of drug-layered or drug-containing core pellets coated with salt (sodium chloride and disodium hydrogen phosphate), hydroxypropyl methyl cellulose (HPMC), and enteric film-coating layer, respectively. The drug-layered core pellets were prepared by a coating layer of omeprazole on inert pellet cores in fluidized bed coater .The multi-layer coated pellets were stable in gastric pH conditions and upper gastrointestinal (GI) tract The drug-layered pellets with multilayer film coatings not only provided delayed and rapid release of omeprazole, but also could provide a good stable property for omeprazole.

In another study, (Daslaniya, et al, 2009) Mesalamine pellets were prepared by coating drug solution on sugar sphere followed by various functional coating. The influence of rate controlling membrane made up of Eudragit RS PO and Eudragit RLPO in combination with delay release polymer seal coating with Eudragit L_{100} in different proportions on drug release kinetics was studied. Pellets were for the various parameter like Physical characteristics, assay and in-vitro dissolution profile.

8. Caffeine as a candidate drug for the current study:-

Caffeine, 1, 3, 7-trimethyl-1H-purine-2, 6 (3H, 7H) - Dione, was chosen to be the active ingredient in the prepared beads sustain release in this study. For physico-chemical properties is a bitter, white crystalline xanthine alkaloid that is a psychoactive stimulant drug and soluble in water with 20 g/l at 20°C and different PH mediums (BASF AG, 2001a) and has a calculated vapor pressure of 0.0000047 Pa at 25°C (BASF AG, 2000a). The Henry's law constant has been estimated to 1.9*1019atm*m3/mole (Swann, et al., 1983).and also caffeine is soluble in different pH media .The melting point is 235 – 239 °C (BASFAG, 2001a), Therapeutically, Caffeine is most widely consumed psychoactive substance, but, unlike many other psychoactive substances, is legal and unregulated in nearly all jurisdictions (Lovett, et al, 2005). Caffeine has diuretic properties when administered in sufficient doses and is used both recreationally and medically to reduce physical fatigue and restore mental alertness when unusual weakness or drowsiness occurs. Caffeine and other methylxanthine derivatives are also used on newborns to treat apnea and correct irregular heartbeats. Caffeine stimulates the central nervous system first at the higher levels, resulting in increased alertness and wakefulness, faster and clearer flow of thought, increased focus, and better general body coordination, later at the spinal cord level at higher doses, low toxicological in human (with or without metabolic activity), simple analytical (In vitro) and appropriates pharmacokinetic properties (Haskell, et al., 2006) Once inside the body, it has a complex chemistry; In addition to that, caffeine is easily analyzable spectrophotometrically at 320 nm in this experiment shown as Figure (5)

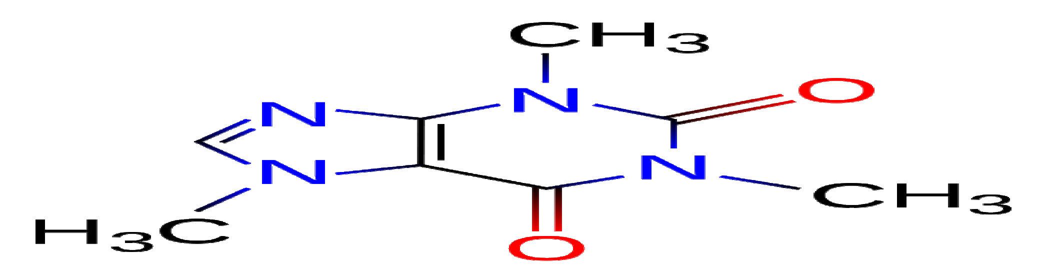


Figure 5. Molecular structure of caffeine **(B.P. 2005)**

9. Objective, Hypothesis and specific aims of the current study:-

9.1. Objective:-

The development and improvement of drug release mechanisms in coated beads is main challenging. Generally, process technically complicated, expensive and time consuming are required to optimize of coating formulation and operating parameters desired to release profiles by investigating the effect of multilayer film coated in different configurations on physical properties and the release profiles of caffeine loaded beads prepared by pelletization technology, Specific objectives included:-

1- The identification of function polymeric compound to adjust drug release profiles from different polymer film coating layers to achieve suitable drug release profiles from coated bead.

2- The stabilization of the film coatings under curing condition and under accelerated stability condition.

9.2. Hypothesis:-

Coated beads were used for 8 hour controlled drug release formulation.The hypothesis of the present study was based on "Effect of multilayer coating film type improve release profile of caffeine by different configurations coated film "To test the hypothesis, used various polymer types films such as Eudragit® E 100 as a protective film coating usually used in seal layer to delayed or retarded release profile of drug and films of different solubility characteristics can be produced ammonio methacrylate copolymer (Eudragit RL 30 D) and ammonio methacrylate copolymer (Eudragit RS 30 D) as a controlled or sustained films were screened for the preparation of coated beads.

9.3. Specific aims:-

1- To Investigation from the effect of different configurations of multilayer polymer film coating on the physical and release profile of caffeine from coated beads

2- To develop and optimize coating process parameters at the production scale and operating conditions (air flow rate, and atomizing air) for achieving a complete film coating and extended-release pattern of coated beads.

3- Investigation the physical and release profile of the model drug from coated beads, in different pH mediums according FDA guidance for industry.

4- To investigate the effect of Ammonio methacrylate copolymer dispersion (Eudragit RL 30 D, RS 30 DPO) in combination with Eudragit E_{100}as a protective polymer in different proportions and their impacts on caffeine release kinetics from coated beads ware studied.

2. EXPERIMENTAL SECTION

2. MATERIALS AND METHODS:-

2.1 Materials

2.1.1. Drug substance

Caffeine anhydrous (Batch No. CAM / 2007/ 041) was purchased from Kores **(INDIA)** (Pharmaceutical and chemical Division)

Synonyms: 1,3,7-trimethyl-2,6-dioxopurine,1,3,7-trimethylxanthine,3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione7-Methyltheophylline

Empirical Formula: C8 H10 N4 O2

Appearance: Odorless, white needles or powder

Density: 1.23 g/cm^3,

Melting point: 227–228 °C (anhydrous).

Boiling point: 178 °C.

The solubility of caffeine in water in 2.2 mg/mL at 25 ^{o}C, 180 mg/mL at 80 ^{o}C, And 670 mg/ mL at 100 ^{o}C.

Chemical structure:-

2.1.2. Excipients:-

Sugar starter cores Spherical sugar granules

Appearance: - White spherical granules with sweet taste, soluble in water

Particle size: 595 – 707 µm

Mesh size (25/30)

Components: sucrose (up to 92%) and maize starch

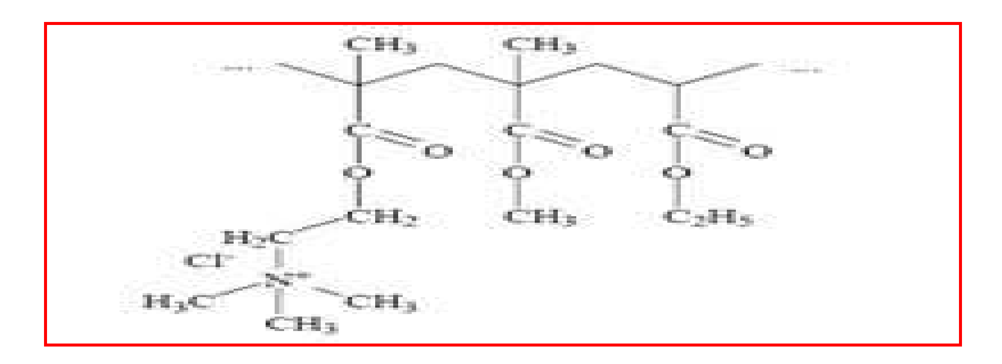
Manufacturing date: 03/2007

EUDRAGIT® E 100:- batch NO (E 060301047) Granules was purchased from dugussa the chemical company (Germany). Eudragit® E is a cationic copolymer composed of dimethyl aminoethyl methacrylate and neutral methacrylic esters in a 1:1 ratio. The tertiary amino group in Eudragit® E makes the polymer gastro soluble and applicable for taste masking. And can also be used for protective coatings or good seal film due to low water vapor permeability or good seal film coat to delayed release of drug. The average molecular weight is approx. 47,000 g/ mol. The polymer is soluble below pH5 due to salt formation of the tertiary amino group of Eudragit® E, which is present in a high quantity in the polymer (Lehmann K, 1974). Above pH 5 Eudragit® E polymers absorb water and swell due to the presence of the hydrophilic amino groups causing disintegration of the coating even at high pH (Lehmann K, 1974).

Chemical structure:-

EUDRAGIT RS PO: -batch NO (GO50838110) is copolymers of acrylic and methacrylic acid esters with a low content in quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable., The average molecular weight is approx. 150,000.:it is colorless, clear to cloudy granules with a faint amine-like odors, white powders with a faint amine-like odors.(Evonik Industries, Pharma Polymers,2008). Targeted Drug Release Area: Time controlled release pH independent Dissolution: Insoluble, Low permeability, pH independent swelling

Chemical structure:-



Eudragit RL 30D (aqueous Dispersion 30 %) (Lot NO. Go30616111**)** (of ethyl acrylate methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups the average molecular weight: approx. 32,000 g/mol. The ammonium groups are present as salts and make the polymers permeable. It is a milky-white liquid of low viscosity with a faint characteristic odors targeted Drug release Area: Time controlled release, pH independent .Dissolution: Insoluble .High permeability. PH independent swelling Characteristics. Customized release profile by combination of RL and RS grades in different ratios .Suitable for matrix structure. (Evonik Industries, Pharma Polymers, 2008).

Chemical structure:-

Triethyl citrate, (Fluka AG CH 9470) is an ester of citric acid. It is a colorless, odorless liquid used as a food additive (E number E1505) to stabilize foams, especially as whipping aid for egg white. In pharmaceutical coatings and plastics. Triethyl citrate is also used as a plasticizer for polyvinylchloride and similar plastics.

Stearic acid ,was purchased from Riedel-deHaën Laboratory chemicals (Germany) it is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor and taste suggesting tallow. It is used as lubricant in making tablets and capsules and also used as an emulsifying and solubilizing agent. (Rowe, et al., 2006).

Sodium lauryl sulfate (SLS), was generously donated by Josue (Jordan). Used as anionic surfactant, detergent, emulsifying agent, tablet and capsule lubricant, and wetting agent (Rowe, et al., 2006).

Hydrochloric acid , 35% it is used in the chemical industry as a chemical reagent in the large-scale production of vinyl chloride for PVC plastic, and MDI/TDI for polyurethane. It has numerous smaller-scale applications, including household cleaning, production of gelatin and other food additives, descaling, and leather processing.

Sodium hydroxide, granulated, synthesis grade (Na OH .M= 40.00) scharlau Chemie S.A it is a white crystalline substance that readily absorbs carbon dioxide and moisture from the air. It is very soluble in water, alcohol, and glycerin.

Potassium dihydrogen phosphate (KH_2PO_4),

Synonyms: Potassium dihydrogen orthophosphate; Potassium phosphate; Mono potassium phosphate

Molecular Formula: KH_2PO_4 Melting point 252.6 ºC

Molecular Weight: 136.08 Water solubility 222 g/L (20 ºC)

Magnesium stearate Mg ($C_{18}H_{35}O_2$)$_2$, also called octadecanoic acid, magnesium salt, is a white substance which is solid at room temperature. It has the chemical formula Mg $(C_{18}H_{35}O_2)_2$. It is a salt containing two equivalents of stearate (the anion of stearic acid) and one magnesium cation (Mg^{2+}), and also used a glidant to avoid sticking during the coating process.

Acetic acid, (CH_3COOH), it is an organic acid that gives vinegar its sour taste and pungent smell. It is a weak acid, in that it is only a partially dissociated acid in an aqueous solution. is a colorless liquid that absorbs water from the environment (hygroscopy).

Sodium acetate, (**$NaC_2H_3O_2$**), also sodium ethanoate, is the sodium salt of acetic acid. This colorless salt has a wide range of use.

Talc (Anti tacking), is recommended in order to avoid sticking during the coating process and also used a glidant for the polymer powder to improve the powder flow into the spraying chamber.

2. Equipments:-

-Laboratory Micro-Processor PH Meter (HANNA instruments).

- Erweka pharma test DT 600, Dissolution tester, Germany.

- Unicam UV2-100 UV/ Vis spectrometer, Unicam, England.

- Ultra-Turrax, Homogenizer, Janke and Kunkel Ika-Turrax, Germany.

- BINDER KBF 240, Stability chamber, BINDER, USA.

- SHIMADZU, Electronic balance, Shimadzu, Japan.

- Nylon filters 0.45µm, PETRATECH, Jordan.

- Oven (Heating Drying oven (50°C) model DHG.

- Mixer (Janke and Kunkel (IKA-Werk).

- Fluid bed coater (Wurster), Umang Pharmatech Ltd.India Modal-USPF 2007.

- Water bath (Hetrowater bath) type SDDSOBIO.

-IkA-Labor technik (motor Magnetic stirrer).

-AE ADAM model AQ T200 (Electronic balance).

-Parasitic pump, Flowteck (Modal -PF01).

3. METHODOLOGY SCETION

3.1. Methods of analysis:-

3.1.1. UVscanning to get maximum λ max:-

In this experiment, the concentration of caffeine will be found with an ultraviolet spectrometer that is relating the absorbance to the concentration. The quantity absorbed depends on the wavelength of radiation and the structure of the compound. An absorption spectrum, also called a wave scan, is necessary to determine the wavelength of absorption of caffeine without interaction with Eudragit® E100. Compounds that contain conjugated multiple bonds; the analysis of these substances followed the same process as the evaluation of UV absorption of pure caffeine.

A sample of each substance was placed in the spectrometer for a scan from 200 nm to 400 nm at λmax 320 nm without interaction of caffeine with Eudragit® E100. As shown in Figure 6.

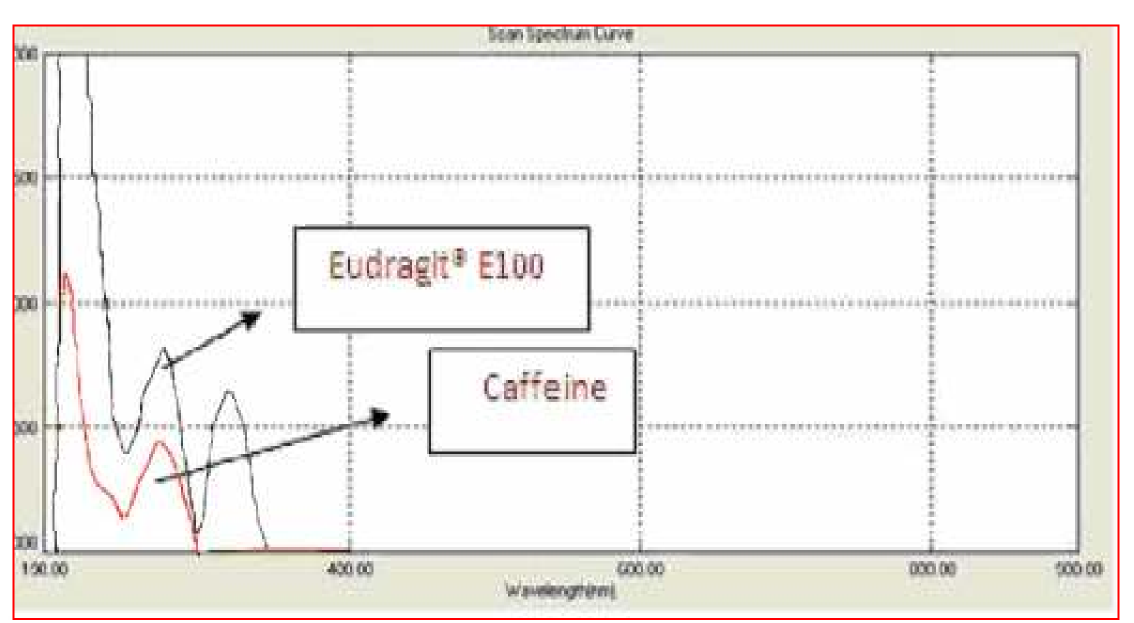


Figure 6.wave scan of caffeine between **(200-400)** nm

3.1.2. Caffeine calibration curve:-

The calibration curve had to be built as a reference for the analysis. This trend line was constructed with five solutions of known concentration of pure caffeine that were evaluated with the spectrometer. Each solution was placed in the machine to measure its absorbance at λmax 320 nm. Then, using Excel, the linear function was made. As shown in Figure 7.

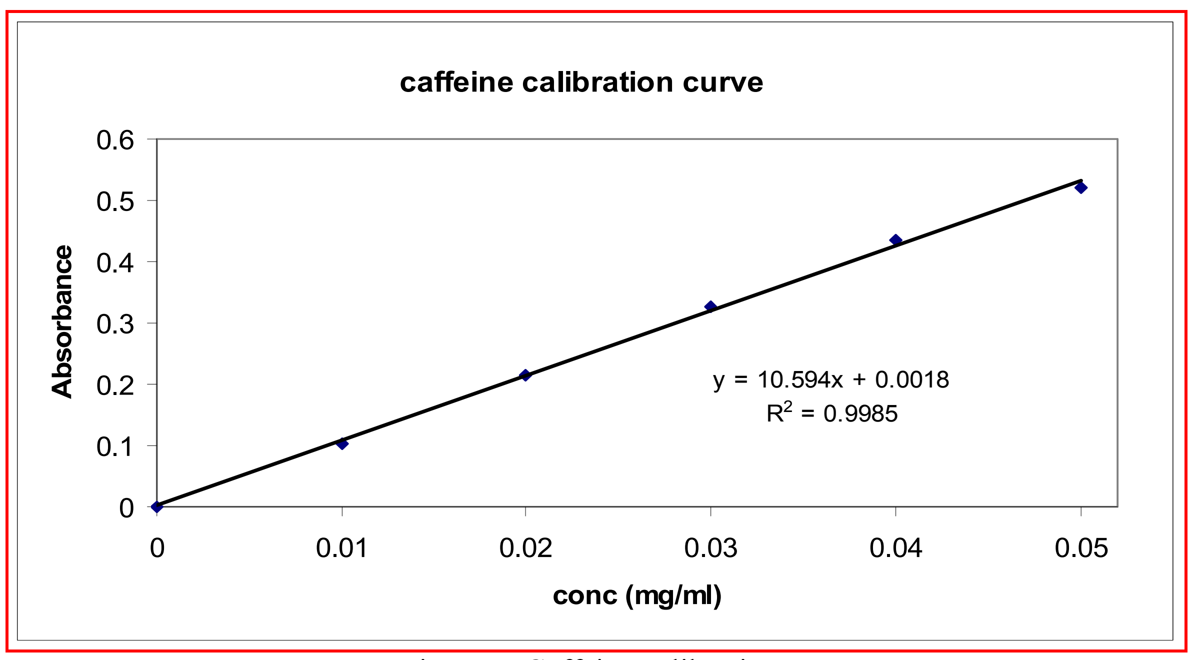


Figure 7. Caffeine calibration curve

3.1.3. Assay of the drug content:-

The drug content of the beads was determined by dissolving an accurately weighed triturated sample of the beads equivalent to 20 mg of caffeine in 500 ml 0.1 N HCL Quantification by UV spectrophotometer using Unicam UV2-100 UV/ Vis spectrometer at λmax 320 nm was performed on the filtrate after filtration by 0.45μm nylon filters. The drug content was carried out in triplicate and the results were expressed as percentages of the theoretical drug content calculated using the following equation: -

Loading efficiency (Drug content (%) = (practical drug content / Theoretical drug content)*100.

3.1.4. Preparation of extended release beads coating:-

Caffeine beads were coated by multilayer various polymer films such as Eudragit® E 100 as a protective film in seal layer without drug or in drug layering and ammonio methacrylate copolymer (Eudragit RL 30 D) and ammonio methacrylate copolymer (Eudragit RS 30 D PO) as a controlled or sustain layer at a ratio (30:70) in a fluidized bed coater equipped (Wurster column), (Umang Pharmatech Ltd .India Modal-USPF 2007), controlled layer were plasticized with triethyl citrate. The drug-layered pellet cores were prepared by spraying caffeine onto inert cores size (595—707 mm).The coating dispersions were sprayed onto 500.00 g as initial core until a weight gain (thickness coat) was achieved accepted value. The film thickness was expressed as the theoretical percentage of the total (solid) weight gained TWG (%)

3.2 Characterization of caffeine-loaded beads

3.2.1. Drug Loading and Seal Coating:-

Approximately 500 g of inert beads (Nonpareil®) were used as initial core to achieve drug loading. The composition of the drug loading dispersion is given in Table 1. The spraying suspension is prepared using an ultra turax. Introduce 203 ml of 0.1 N HCL then add Eudragit® E 100 30 gram and dissolve it in portions at high mixing speed (1000-1500 rpm) and filtration of this solution .then adds Mg stearate 10 gram and caffeine drug 5 grams in portion to this solution until completely dissolve. When no more solid on the surface add stearic acid 4 grams in portion and using of homogenizer to obtain a homogenous suspension , Finally add SLS in portions and mix until you get a homogenous suspension. And pass the spray suspension through a 0.5 mm sieve. The operating parameters for both drug loading (caffeine) and seal coating (without caffeine) are given Table 2, Seal coating was provided by applying suspension similar to the drug loading suspension without caffeine following the seal coating beads were dried for 10 minutes at 45° C in the coating chamber, Seal coating was applied to drug loaded beads

primarily to avoid the leaching of drug into controlled release coating and on starter coat to smoothness surface of beads. The desired size **(25/30)** mesh of the drug loaded beads was used for coating.

Table 1. Composition of drug loading dispersion (caffeine layer) or (seal layer) without caffeine

Coating Ingredients	Qty (g)
Eudragit E® 100 granules	30 grams
Mg stearate	10 grams
Streaic acid	4 grams
SLS	3 grams
Caffeine (Drug)	5 grams
0.1 N HCL up to	203 ml

All quantities are in grams

Table 2. Processing conditions for Drug layering and Seal layering

Machine	Fluid bed coater (Wurster),Umang Pharmatech Ltd.India	
Parameters	**Drug layering**	**Seal layering**
Type	**bottom spray**	**bottom spray**
Spray nozzle diameter	**0.8 mm**	**0.8 mm**
Bed Size	**500.0 gm**	**500.0 gm**
Inlet temperature	**60-65 °C**	**60-65 °C**
Outlet temperature	**42-50 °C**	**38-45 °C**
Product temperature	**55°C**	**55°C**
Atomizing air pressure	**1.0 bar**	**1.5 bar**
Coating spray rate	**2.0 ml/min**	**2.0 ml/min**
Spray rate	**2.0 g/min**	**2.0 g/min**
Spray time	**140 min-160min**	**140 min-160min**
Peristaltic pump (rpm)	**0.5-2 rpm**	**0.5-2 rpm**
Secondary drying	**45 °C/10 min**	**45 °C/10 min**

3.2.2. Controlled Release Coating: -

The controlled polymer dispersion prepared was employed for providing controlled release profile of caffeine. The composition of controlled Coating suspension is given in Table 3, the operating parameters such as, spray rate, and atomizing pressure were introduced as dependent factors. Following coating, the beads were dried for 15 minutes in fluid bed at 40 °C to avoid twining and aggregation and cured further in an oven at 50 °C for 1 month & Accelerated stability condition for 3 months at 40°C/ 75 % RH the operating parameters of controlled coating were given in Table 4 .

Table 3. Composition of controlled release coating suspension

Coating materials	Qty (g)
Eudragit RS 30D PO 70% + 30% RL 30 D	35 g RS 30 D PO +15 g RL 30 D
Triethyl citrate	2.5 grams
Talc	5.0 grams
Dilution with water up to	375 ml

All quantities are in grams

Table 4. Processing conditions for controlled release coating

Machine	Fluid bed coater (Wurster),Umang Pharmatech Ltd.India
Parameters	Units
Type	bottom spray
Spray nozzle diameter	0.8 mm
Batch Size	500 gm
Inlet air temperature	65°C
Product temperature	55 °C
Outlet temperature	50 °C
Coating spray rate	2.0 or 4.0 ml/min
Spray pressure	1.5 bar
Spray time (min)	180-260 min
Spray rate	2.0 - 3.0 g/min
Peristaltic pump	0.5- 4 rpm
Secondary drying	40°C /15 min

3.3.3. In-vitro caffeine release (dissolution):-

Dissolution of caffeine from the beads was tested by using 0.1 N HCl in drug coating and Seal Coating in for 2 hr and 0.1 N HCl for 2 hr , phosphate buffer pH 6.8 in for 6 hr (USP XXIX) as dissolution medium in controlled coating were subjected to dissolution to determine the in-vitro release profile. For this purpose, an accurately weighed amounts of the beads (of size 595-707 Mm) equivalent to 20 mg caffeine were placed inside the baskets of USP I dissolution apparatus (Erweka pharma test DT 600, Dissolution tester).The dissolution test was performed in 1000 ml of dissolution medium at 37 ºC at 50 r.p.m. Aliquots (5ml) were withdrawn at predetermined fixed time intervals (5, 10, 15,20,30,45 min and 8 hour). An equal volume of fresh media, equilibrated at the same temperature, was added after each sampling to maintain sink conditions. Withdrawn samples were filtered through 0.45 µm nylon filters and analyzed spectrophotometrically by Unicam UV2-100 UV/ Vis spectrometer at (λ = 320 nm) and the results were expressed as cumulative percentages of the dissolved drug.

3.3.4. In-vitro caffeine release in various dissolution media:-

In vitro dissolution studies were performed on Erweka pharma test (DT 600, Dissolution tester, Germany) employing basket method. The volume of dissolution medium used was 1000 ml and various dissolution media employed were PH 1.2 (0.1N) HCL, pH 4.5 acetate buffer and pH 6.8 phosphate Buffer for 8 hours. The temperature was maintained at 37°C and rotations per minute were maintained at 50 rpm, Then at each interval of time (5, 10,15, 20, 25,30,45,60,120 minutes,8 hr), 5ml of samples were collected and replaced with same amount of the solution. Samples withdrawn were filtered through Nylon filters 0.45µm and analyzed at (λ = 320 nm) using UV visible double beam spectrophotometer, in **configuration (1)** consist from seal layer on the starter core, drug layer, seal layer and controlled layer in top coat, **configuration (2)** consist from from seal layer on the starter core , drug layer and controlled layer in top coat,

configuration (3) consist from, drug layer and controlled layer in top coat, **configuration (4)** consist from drug layer, seal layer and controlled layer in top coat as shows in figures (16, 17,18 and19).

3.3.5. Stability condition (stress condition) in this study:-

Caffeine coated pellets were stored in open and closed vials in stability chamber. Caffeine release from the pellets was measured before and after 3 months at (40 °C and 75 % RH), based on our experience.

3.2.6. Curing condition (thermal condition) in this study:-

Caffeine coated pellets were stored in Petri - dish at 50°C in an oven Caffeine release from the pellets was measured before and after 1 month at 50°C ,based on our experience.

4. RESULTS AND DISCUSSION

4.1. Effect of stability studies:-

4.1.1. Accelerated stability condition (stress condition):-

Instability during long term storage of the film remains one of the major challenges when using aqueous polymer dispersions for controlled release coatings. The stability of the coated beads was tested by accelerated stability testing. The coated beads were subjected to the conditions at 40°C / 75 % RH. Temperature or humidity dependent changes in the drug release profiles. To improve film formation during coating/curing and/or hinders further polymer particle coalescence during long term storage. Importantly, the drug release patterns from these beads significantly change upon close and open storage for 3 months in stability chamber in 0.1 N HCl. And also in phosphate buffer pH 6.8 the effect being more pronounced in pH 6.8 phosphate buffer as shows in figures (12, 13, 14, and 15) **.**

This phenomenon can probably be attributed to further polymer particle coalescence because the mobility of the polymer chains significantly increases with increasing temperature and water acts as a plasticizer and is mandatory for the capillary forces driving the particles together**.** Since plasticizer is essential for mobility of the macromolecules, the type of plasticizer might affect the degree of polymer particle coalescence in the film coatings and/or the release profile. But longer periods of thermal and humidity challenge are useful during development to confirm that maximum retardation of release has been achieved.

4.1.2. Curing condition (thermal treatment):-

A thermal treatment (called curing) is generally performed after coating. The idea is that at elevated temperature the mobility of the macromolecules is increased and, thus, particle coalescence facilitated. In some cases, curing is also conducted at elevated relative humidity (RH) to facilitate film formation.

Figures (8, 9, 10, 11) shows the release of the model drug caffeine from beads coated with methacrylate copolymer Eudragit® (RL, RS), as a function of the curing conditions 1 day, 1, 2 week, 1 month in an oven at 50 °C.

The lower drug release rates observed after curing at elevated temperature suggest a higher degree of polymer particle coalescence. In this study curing for 1 day at 50°C in an oven was sufficient to provide a release profile insensitive to further temperature challenge and also shorter curing times may be used to identify the minimum curing time.

4.2. Statistical analysis of curing condition (thermal treatment):-

The dissolution profiles of coated beads stored at 50°C in an oven were evaluated periodically. The fit factors f1 and f2 are two indices that compare the dissolution profiles of initial formulation to that of a test formulation. These fit factors allow the systematic comparison of dissolution profiles at different time points, in **configurations (1) multilayer coating** consist from seal layer on the starters core, drug layer, seal layer and controlled layer in top coat **configuration (2)** consist from from seal layer on the starters core , drug layer and controlled layer in top coat **configuration (3)** consist from, drug layer and controlled layer in top coat **configuration (4)** consist from drug layer, seal layer and controlled layer in top coat

The dissolution profile of pellets was considered as initial profiles of sample pellets collected periodically during the stability studies were considered as test profiles. The f1 and f2 values were computed by the equations given below:-

$$F_2 = 50 \log [[1+ (1/n) \sum^{n}_{t=1} (R_r - T_t)^2]^{-0.5}]100].$$

$$F1 = \sum^{n}_{t=1} Rt\text{-}Tt / \sum_{t=1} RT*100.$$

Factor, f1 and exponentially by fit factor, f2. Fit factor fit is zero when the test and initial profiles are identical and increases proportionally with dissimilarity between two profiles. Fit factor f2 is 100 when the test and initial profiles are identical and decreases proportionally with dissimilarity

between two profiles. In the present study, dissolution profile at zero time point represents the initial curve and the dissolution profiles at different time intervals of stability studies represent generally similarity factor in the range of 50-100 is acceptable according to US FDA.

Rate and extent of release of caffeine from the coated beads stored in an oven at 50° C decreased with time as shows in figures (8.9, 10, and 11). At higher temperatures, the reduced rate of release (increase in f1value and decreased f2 values) shows in tables (4, 5, 6.and7) .The process is further supported by evaporation of water and the coalescence of the polymer particles into a homogenous film.

The films become more homogenous upon aging due to further gradual coalescence. The plasticizer might have also escaped from the system at elevated temperature leading to decreased free-volume in the films (Petereit, H.U. and W. Weisbrod, 1999).

Configuration (1)

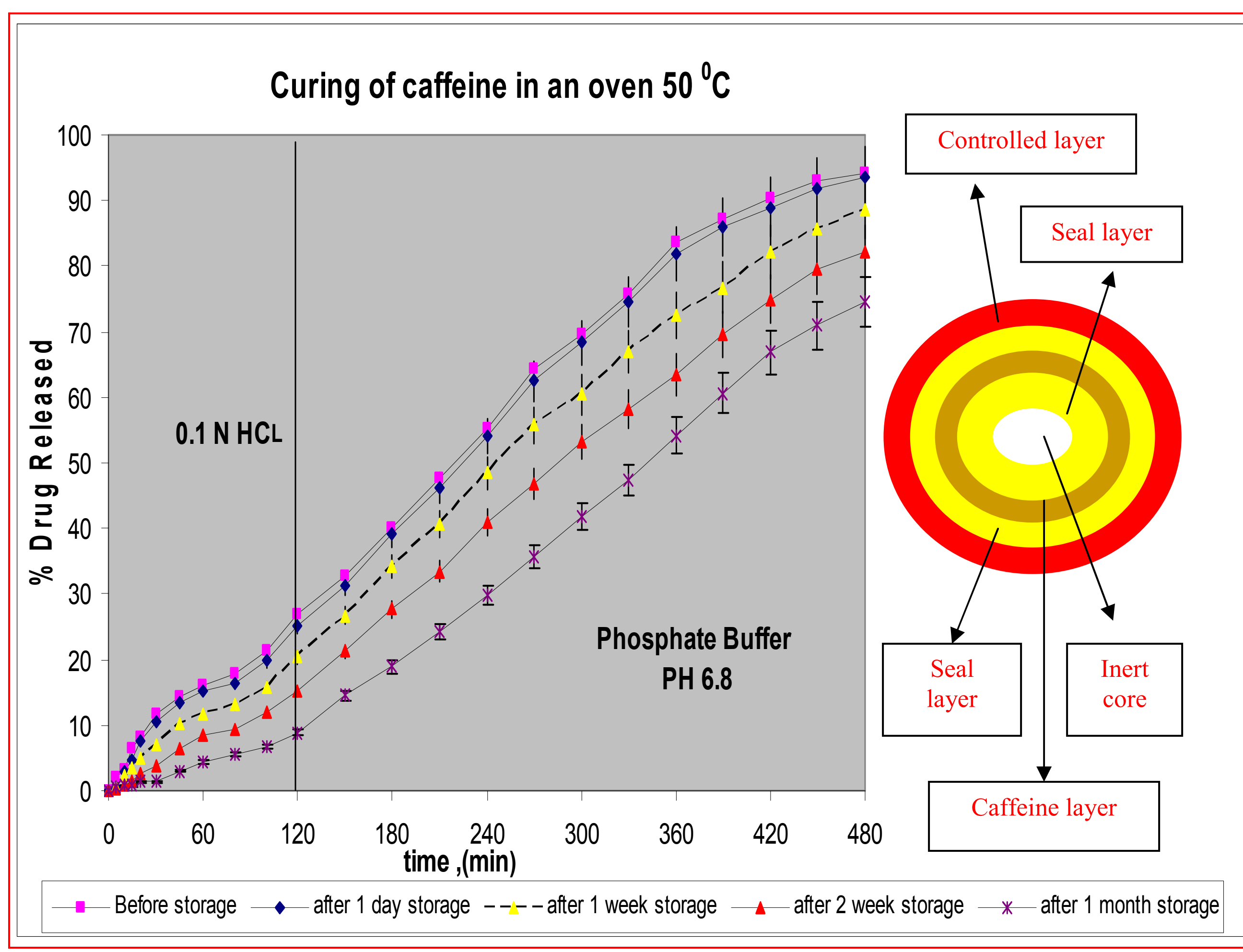


Figure 8. Effects of the curing conditions on caffeine release from pellets coated with methylacrylate copolymer upon exposure (a) 0.1 N HCl, (b) phosphate buffer pH 6.8, Stored at 50 °C **configuration (1)**

Configuration (2)

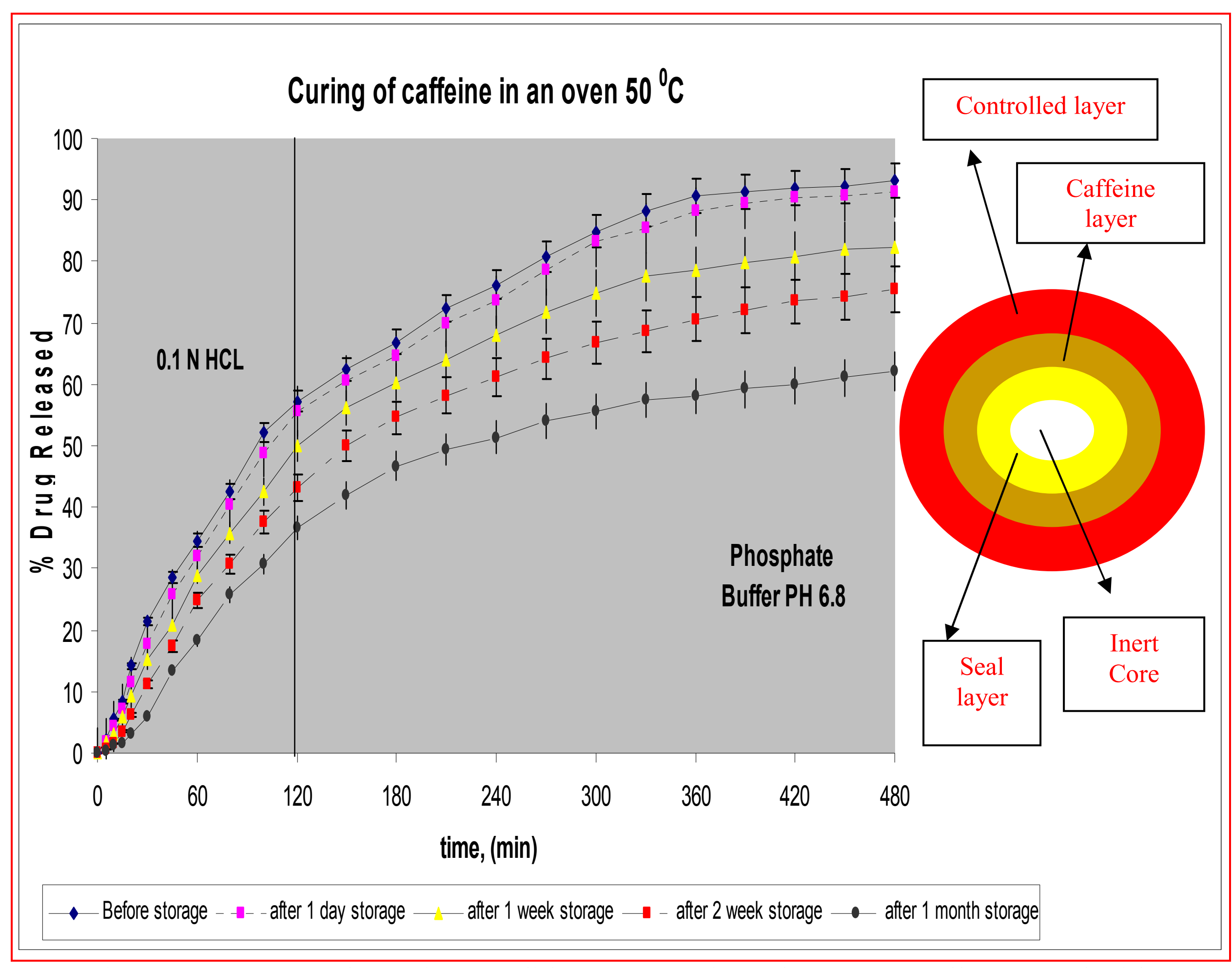


Figure 9. Effects of the curing conditions on caffeine release from pellets coated with methylacrylat copolymer upon exposure (a) 0.1 N HCl, (b) phosphate buffer pH 6.8, Stored at 50 °C **configuration (2)**

Configuration (3)

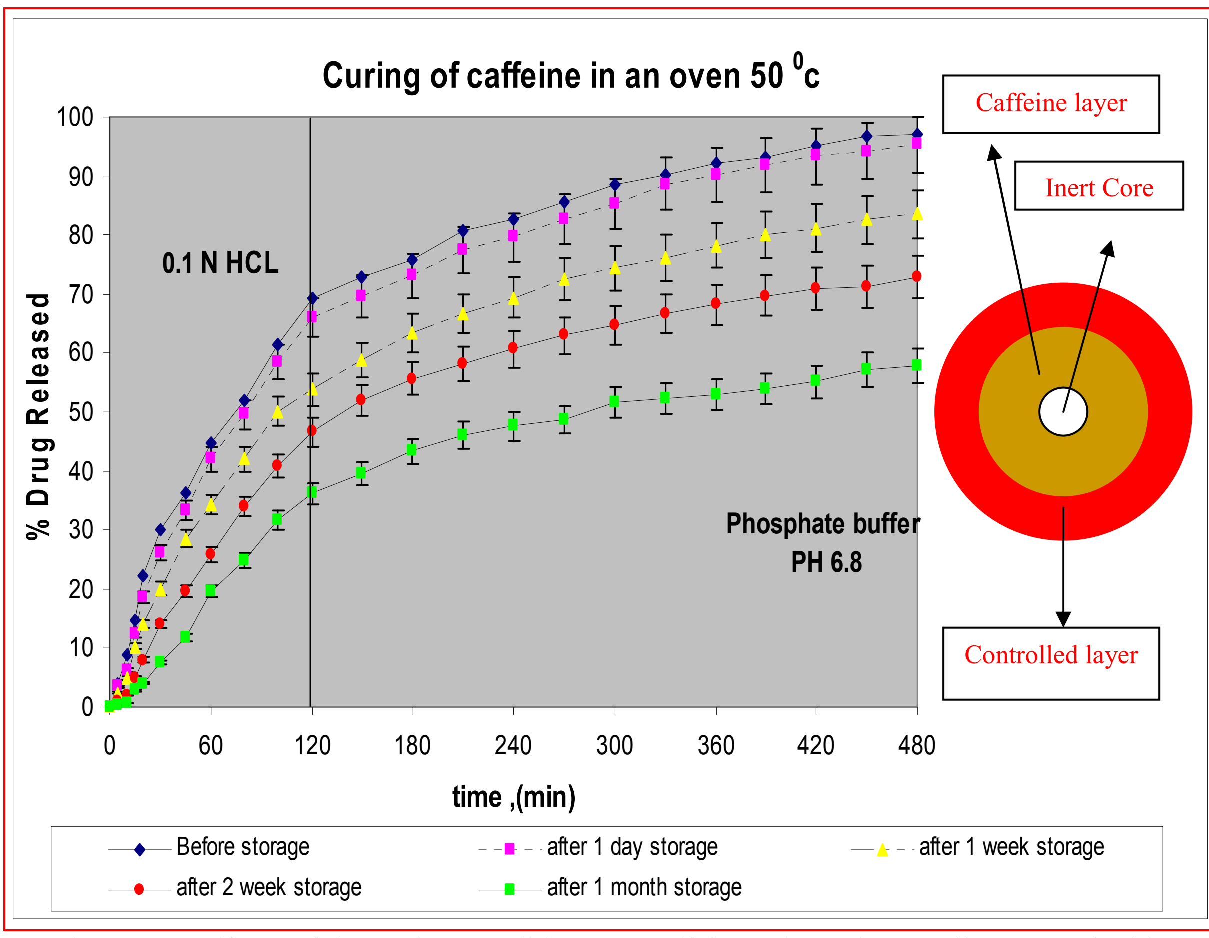


Figure 10. Effects of the curing conditions on caffeine release from pellets coated with methylacrylate copolymer upon exposure (a) 0.1 N HCl, (b) phosphate buffer pH 6.8, Stored at 50 °C **configuration (3)**

Configuration (4)

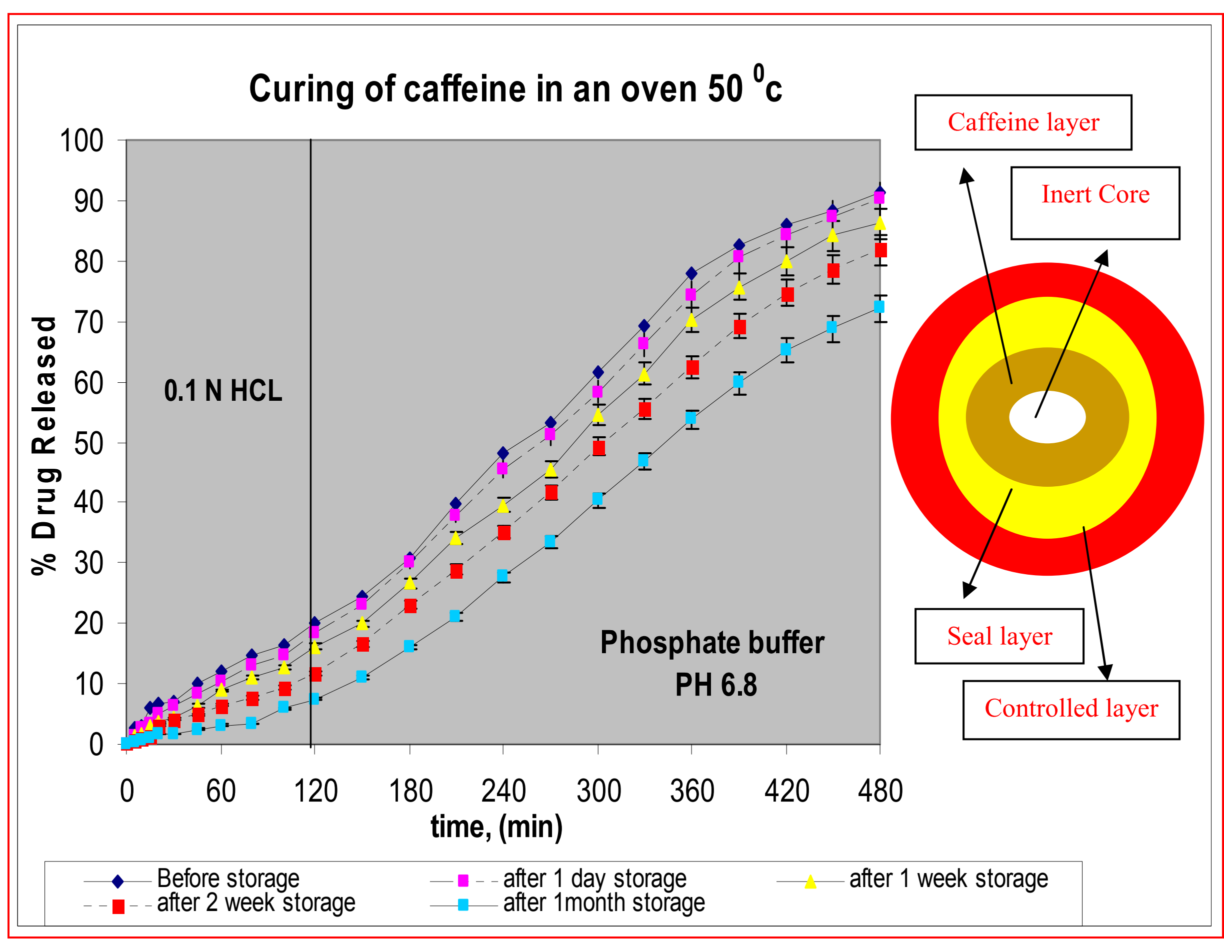


Figure 11: Effects of the curing conditions on caffeine release from pellets coated with methylacrylate Copolymer upon exposure (a) 0.1 N HCl, (b) (b) phosphate buffer pH 6.8, Stored at 50 °C **configuration (4)**

Configuration (1)

Table 5. F2, F1 values of caffeine dissolution profiles from beads stored at 50 °C in an oven

Time	Similarity Factor (f2)	Difference Factor (f1)
1 day	98.34	1.37
1week	78.25	6.39
2 week	71.23	15.17
1 month	68.27	25.24

Configuration (2)

Table 6. F2, F1values of caffeine dissolution profiles from beads stored at 50 °C in an oven

Time	Similarity Factor (f2)	Difference Factor (f1)
1 day	92.26	2.21
1 week	63.34	13.32
2 week	53.87	22.46
1 month	40.26	50.17

Configuration (3)

Table 7. F2, F1 values of caffeine dissolution profiles from beads stored at 50 °C in an oven

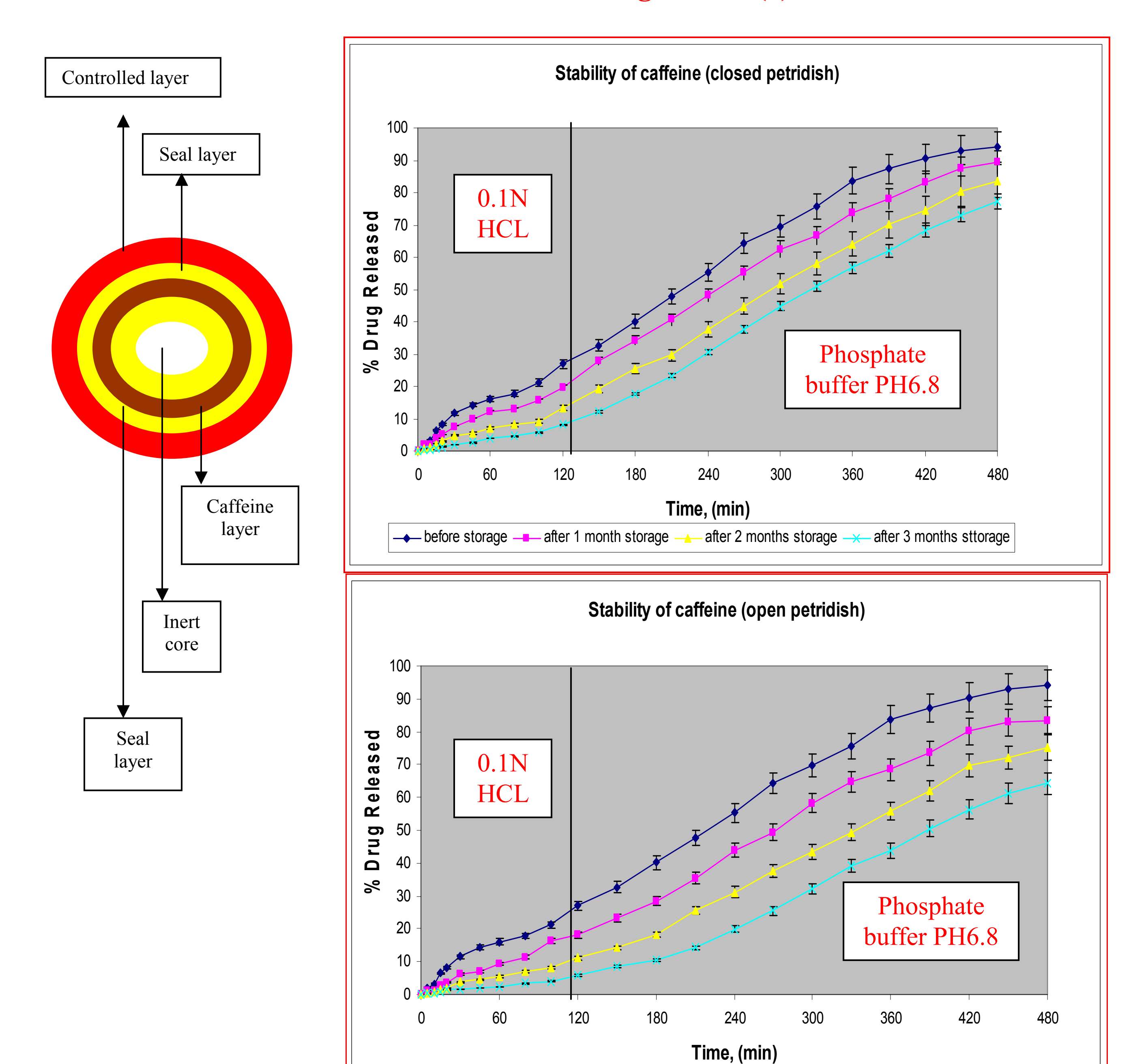
Time	Similarity Factor (f2)	Difference Factor (f1)
1 day	98.34	1.37
1week	78.25	6.39
2 week	71.23	15.17
1 month	68.27	25.24

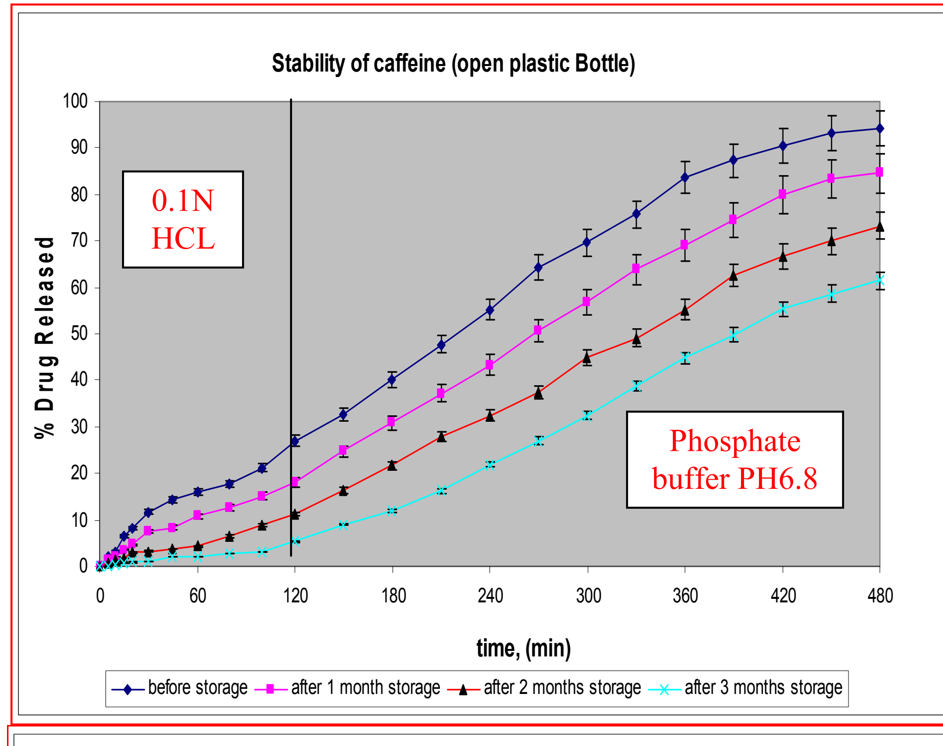
Configuration (4)

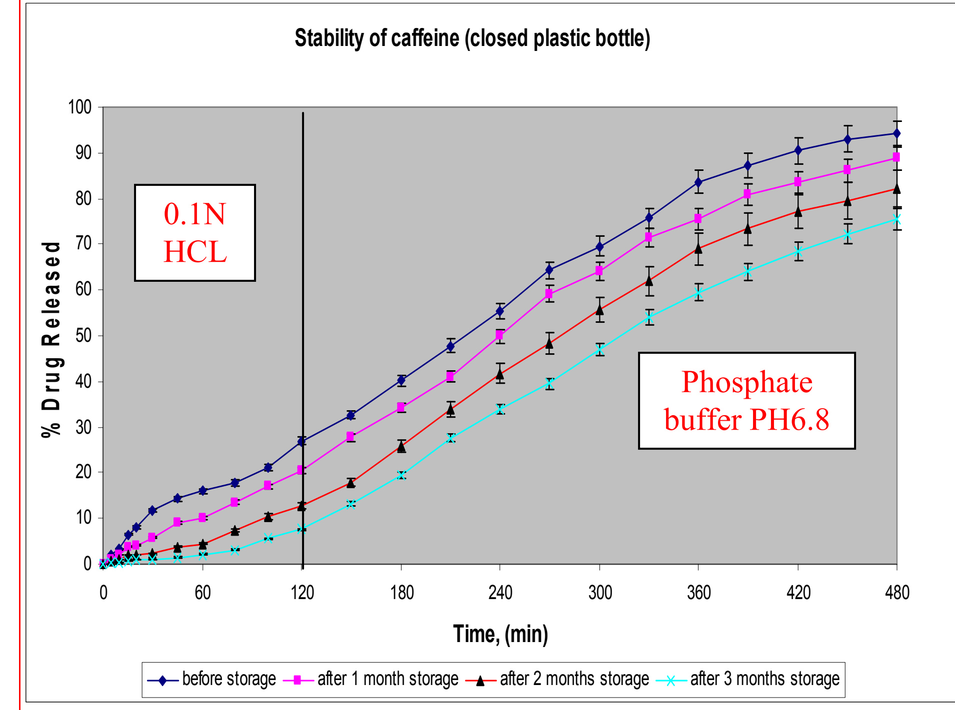
Table 8. F2, F1values of caffeine dissolution profiles from beads stored at 50°C in an oven

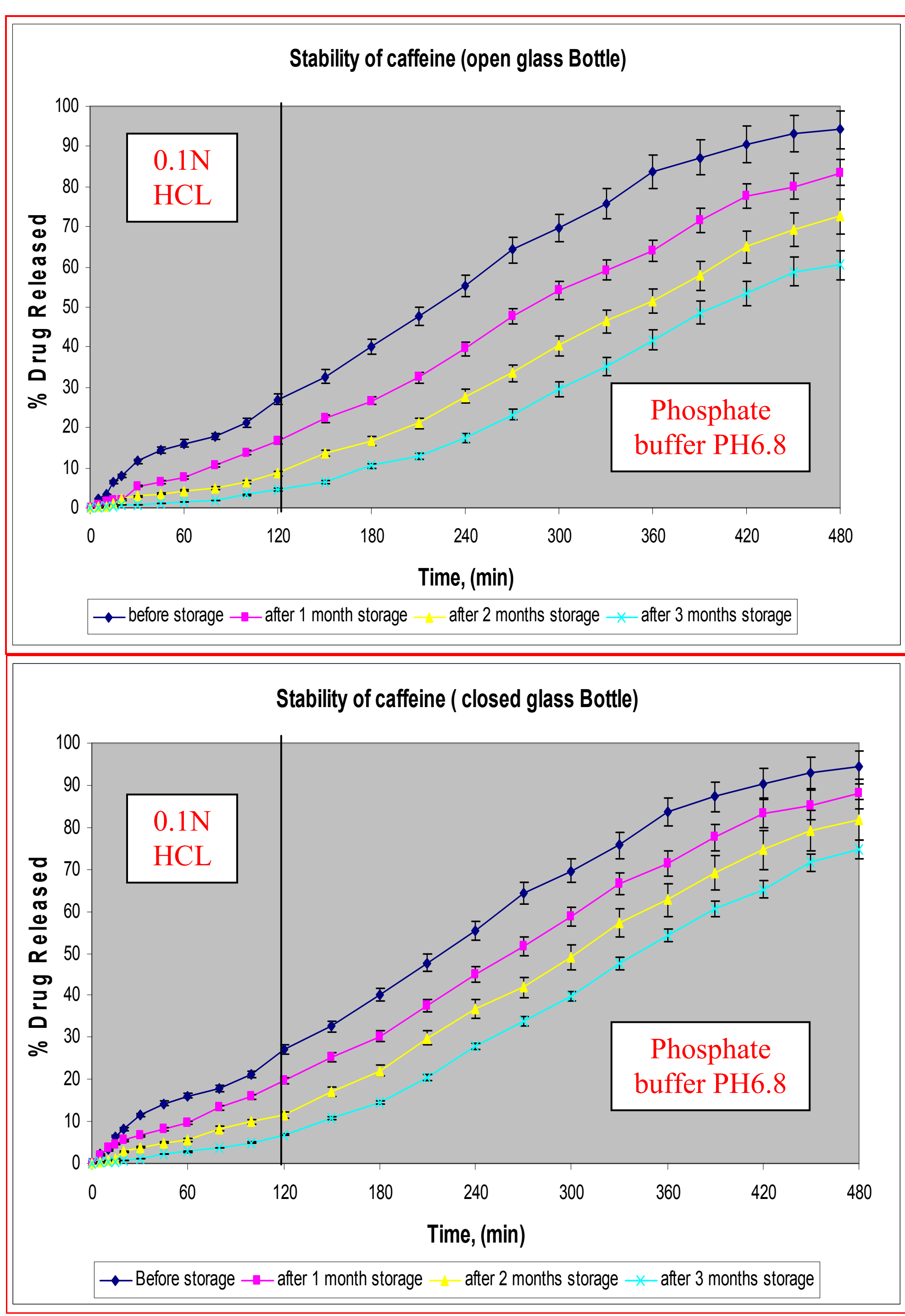
Time	Similarity Factor (f2)	Difference Factor (f1)
1 day	92.65	2.54
1 week	58.45	17.26
2 week	46.37	33.54
1 month	50.85	20.33

Configuration (1)



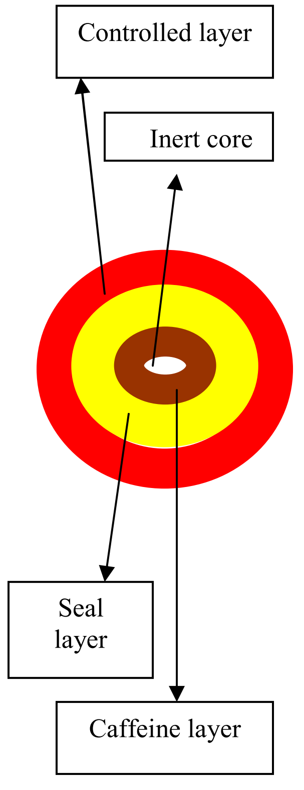

Stability of caffeine (open plastic Bottle)
% Drug Released
0.1N HCL
Phosphate buffer PH6.8
time, (min)
before storage
after 1 month storage
after 2 months storage
after 3 months storage

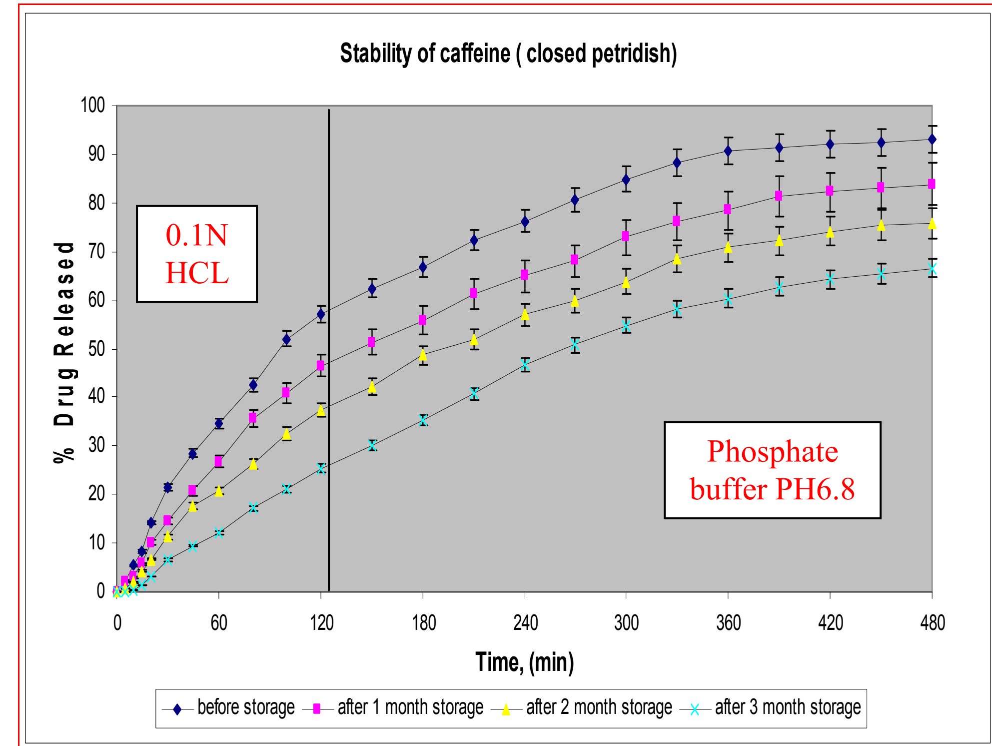

Stability of caffeine (closed plastic bottle)
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0.1N HCL
Phosphate buffer PH6.8
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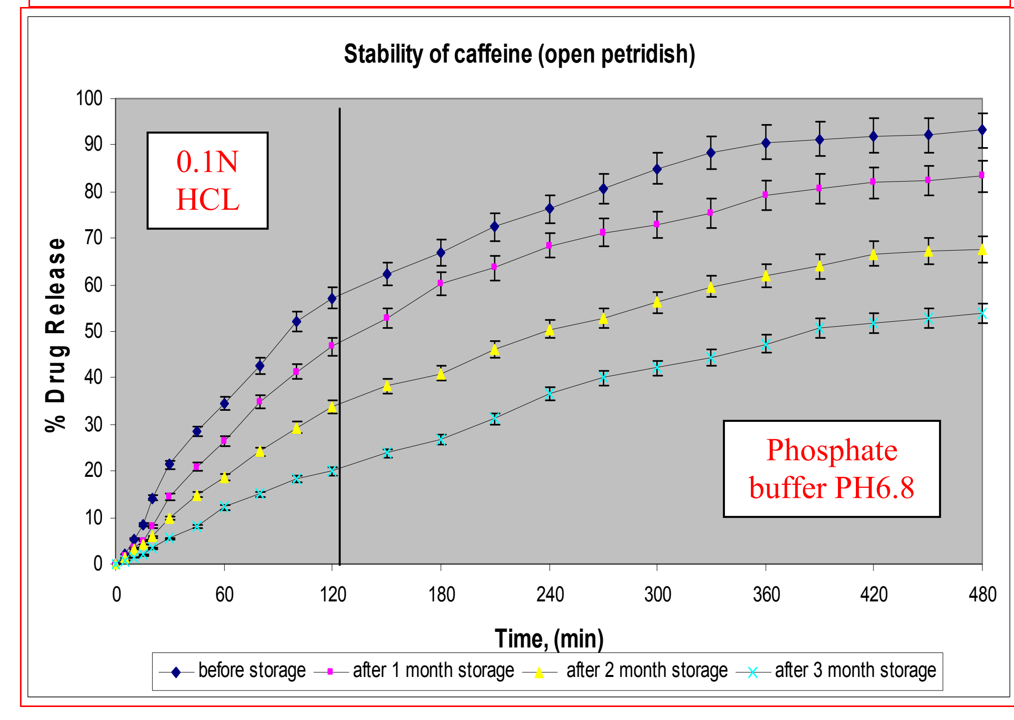


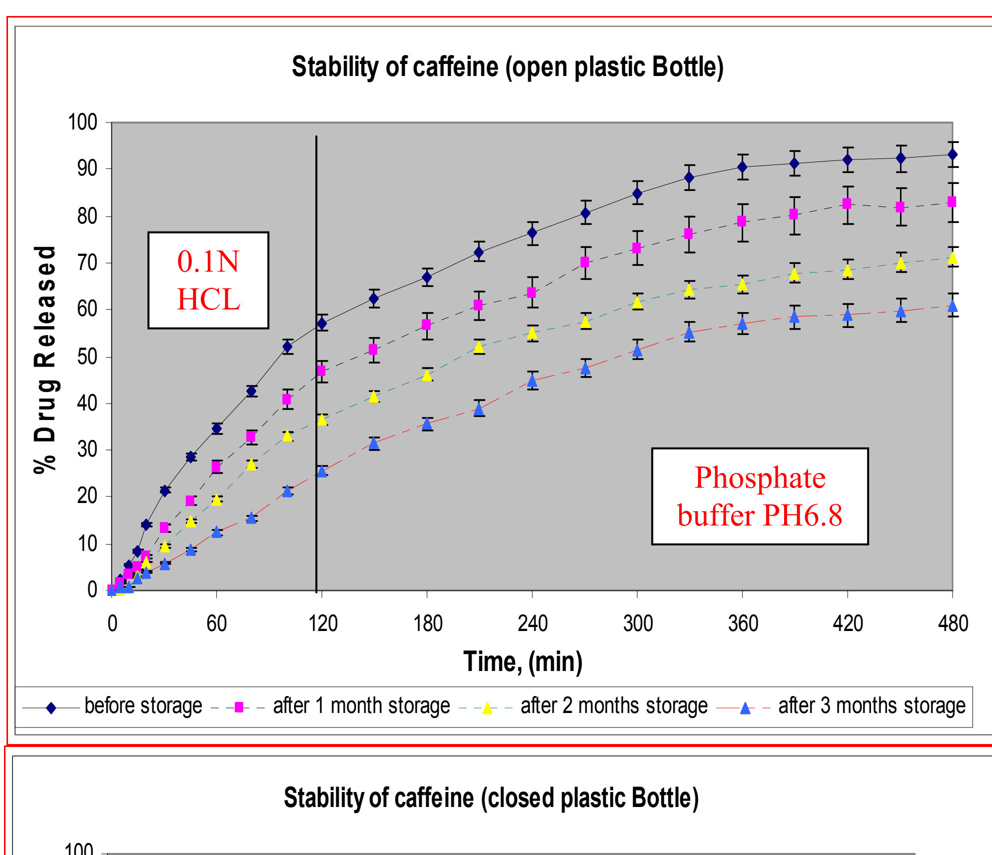
Figures 12. Release profiles of caffeine from multiparticulate beads stored At 40 DGC / 75% RH in different container after 3 months **Configuration (1)**

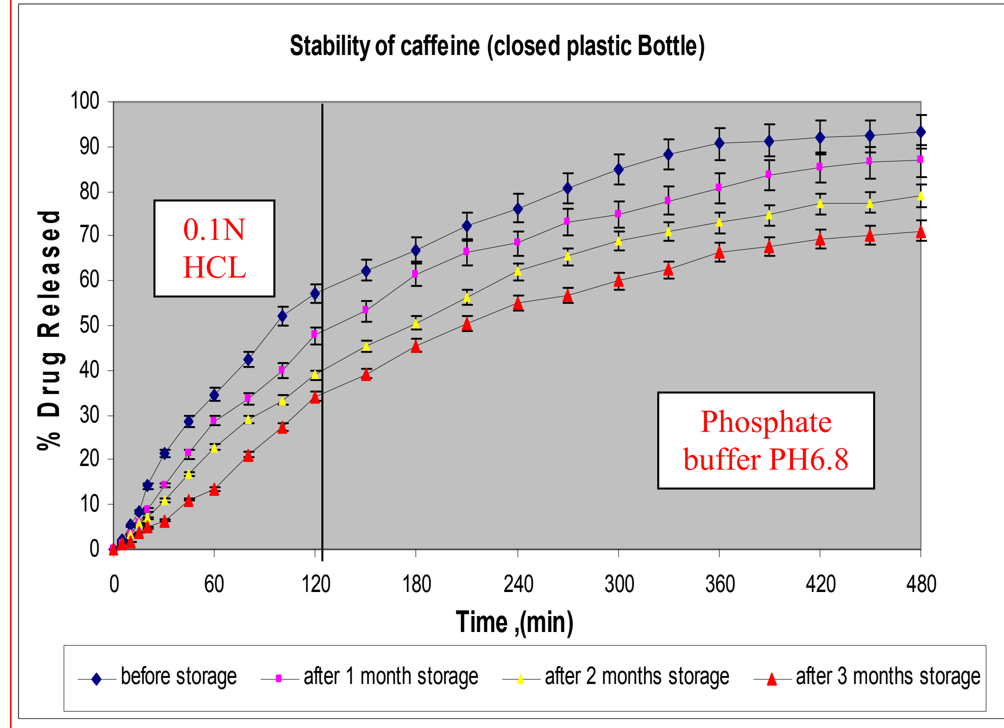
Configuration (2)





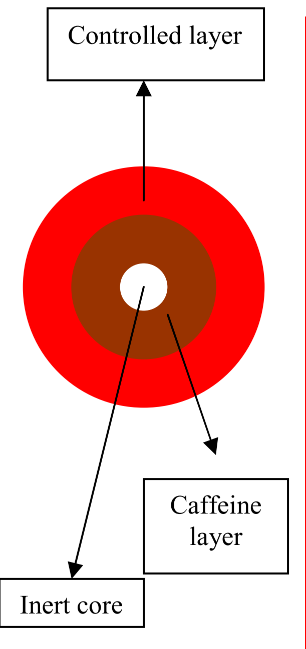


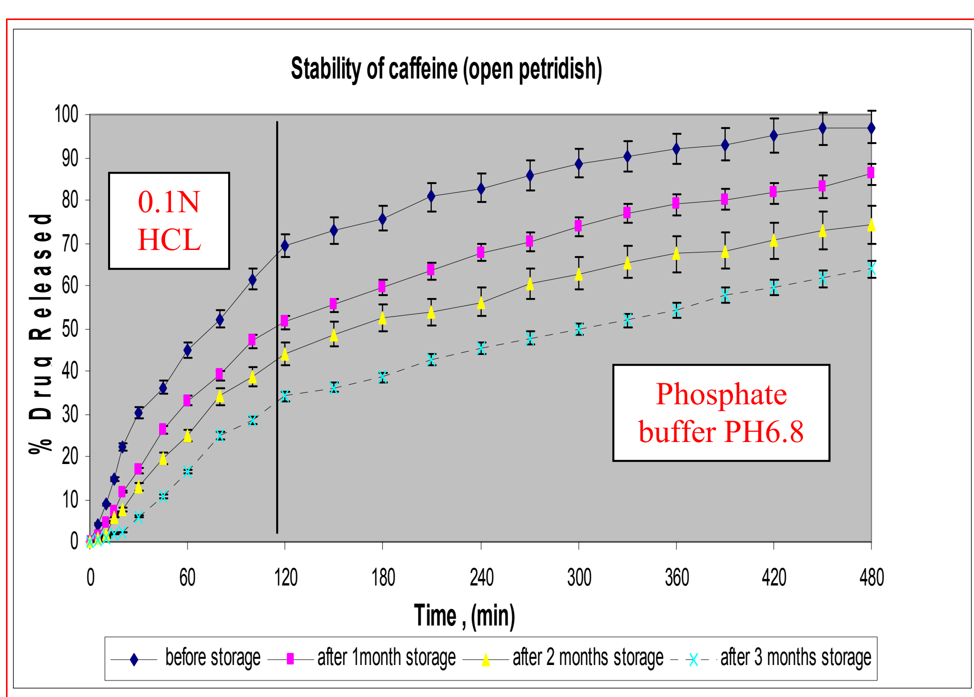


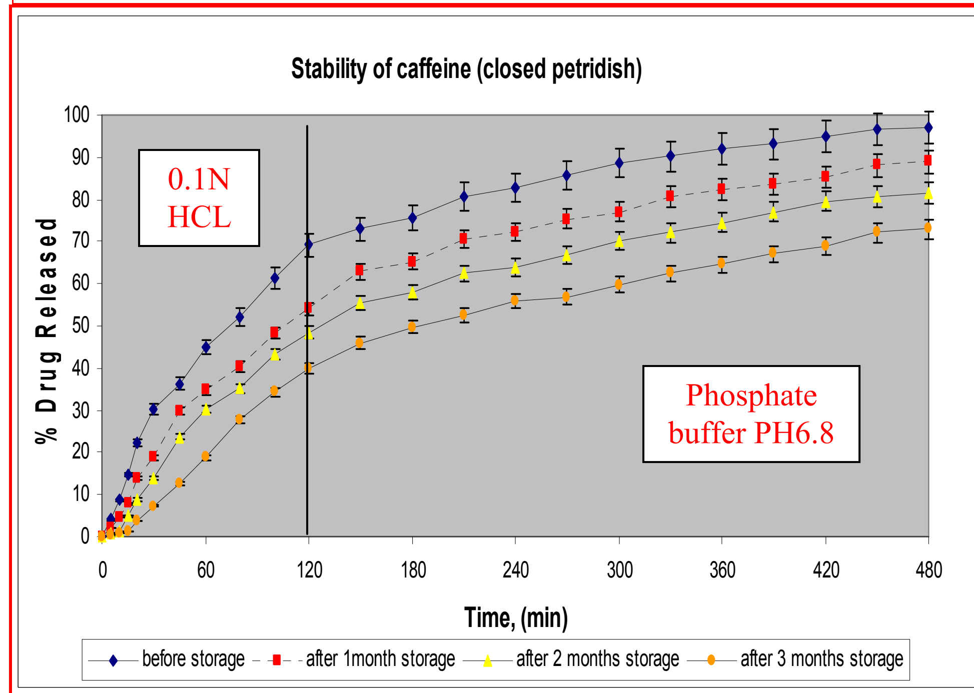


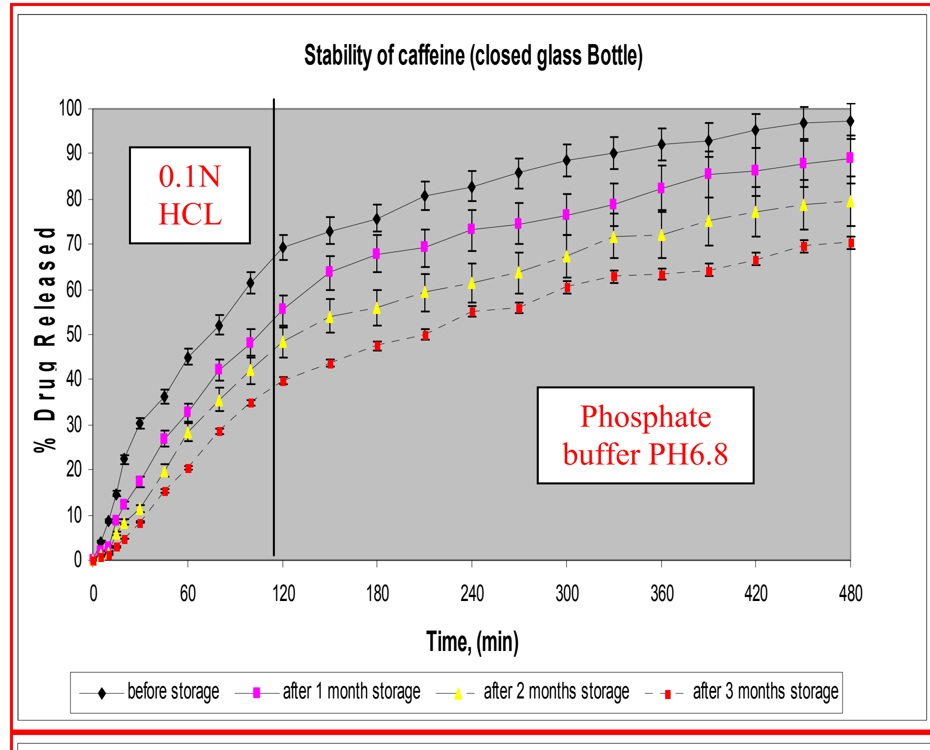
Figures 13. Release profiles of caffeine from multiparticulate beads storedat 40 DGC / 75% RH in different container after 3 months **Configuration (2)**

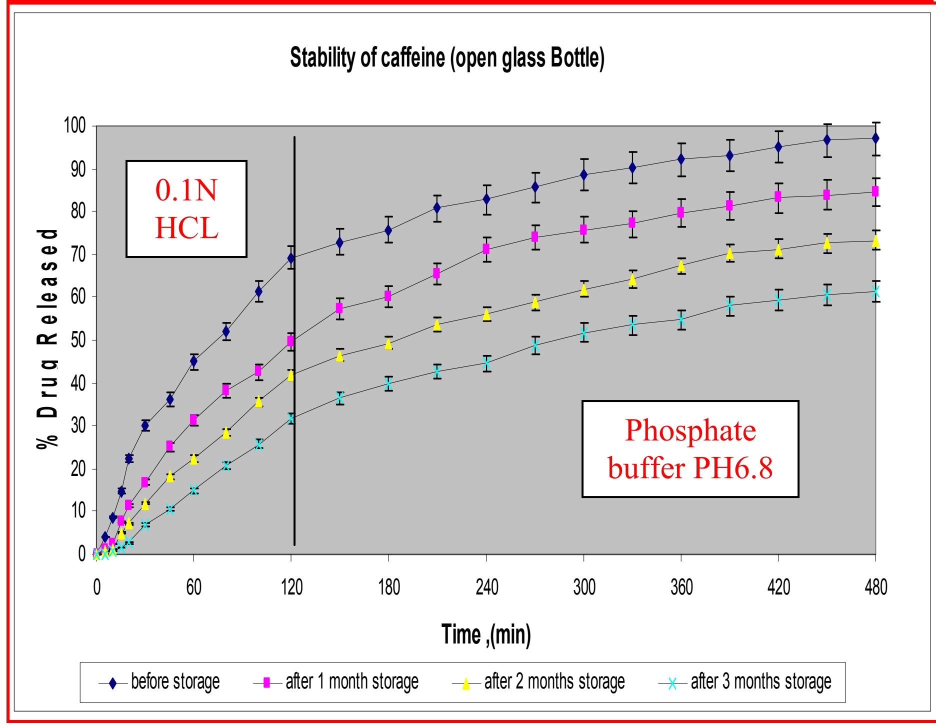
Configuration (3)

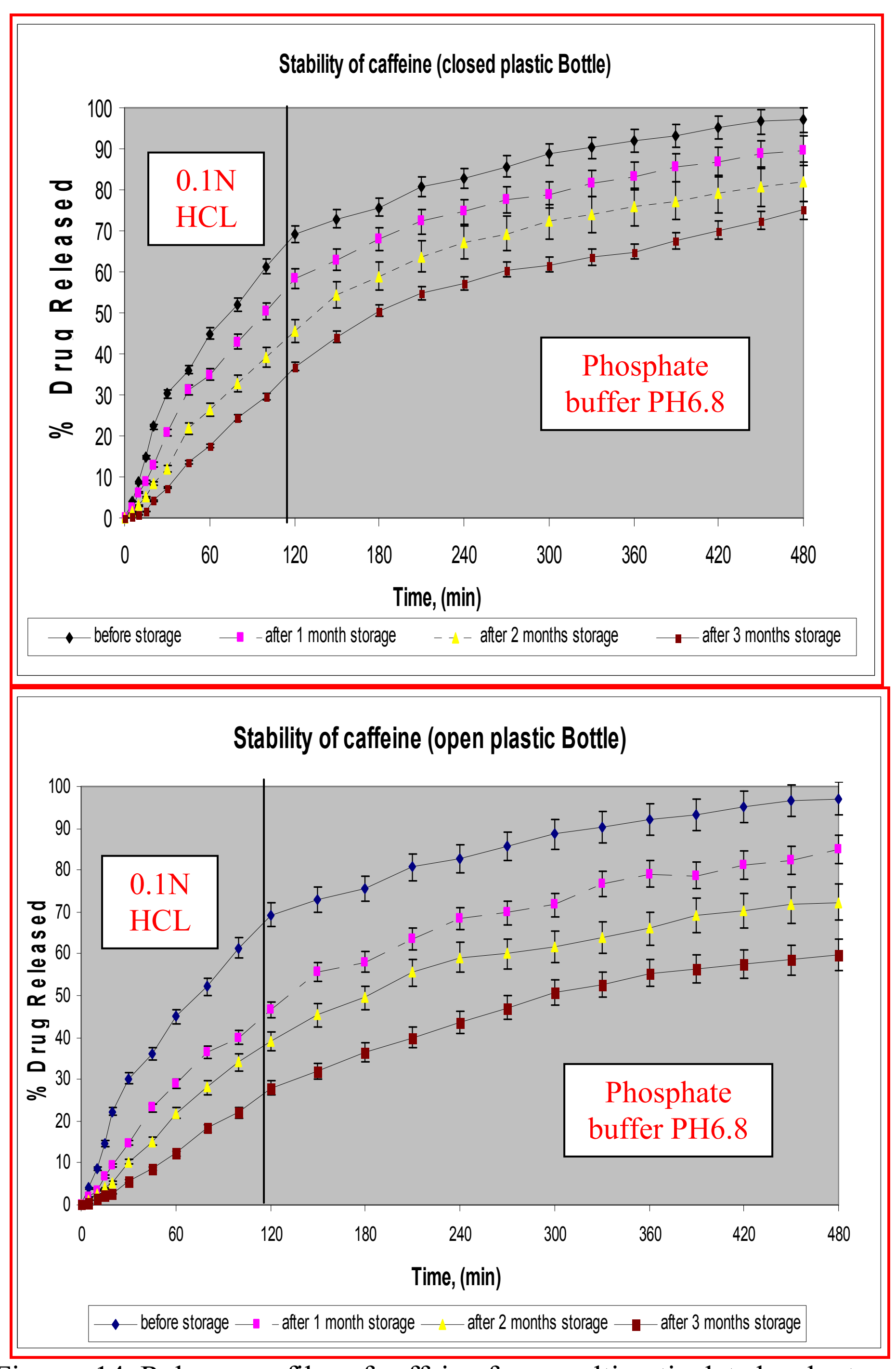






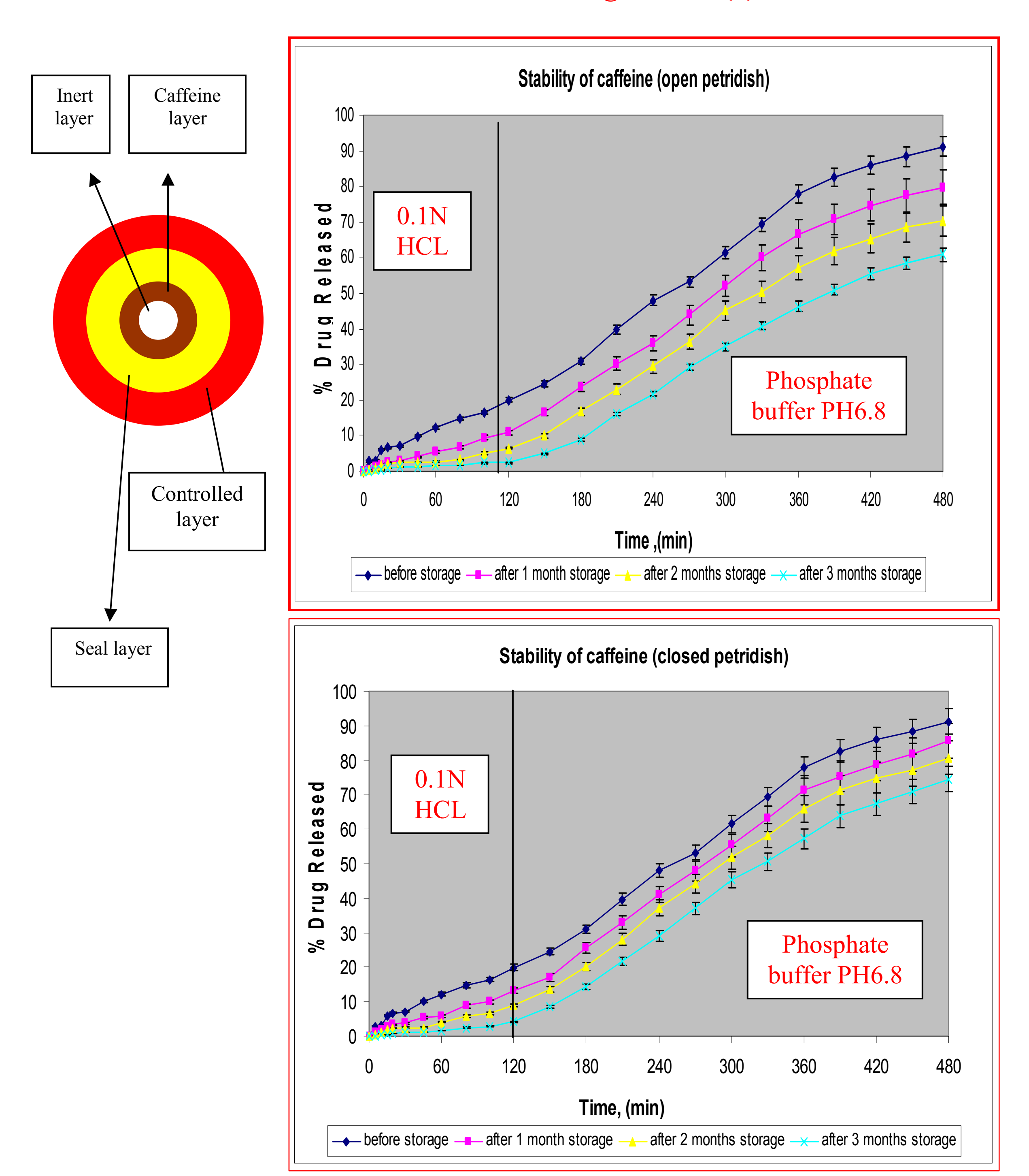

Stability of caffeine (closed glass Bottle)
0.1N HCL
Phosphate buffer PH6.8
% Drug Released
Time, (min)
before storage
after 1 month storage
after 2 months storage
after 3 months storage

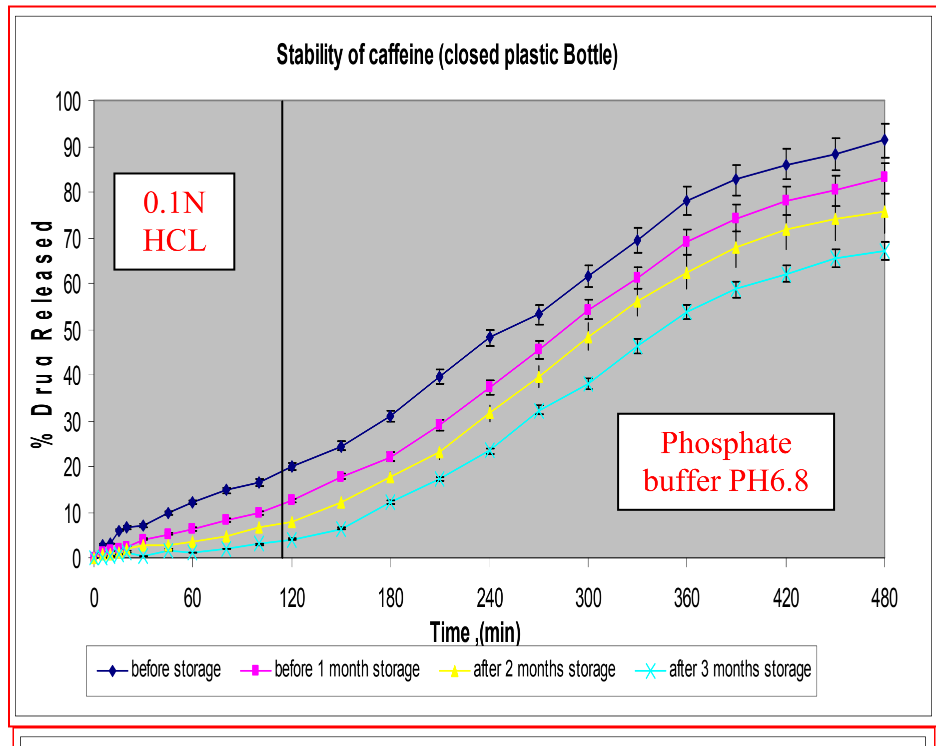

Stability of caffeine (open glass Bottle)
0.1N HCL
Phosphate buffer PH6.8
% Drug Released
Time ,(min)
before storage
after 1 month storage
after 2 months storage
after 3 months storage

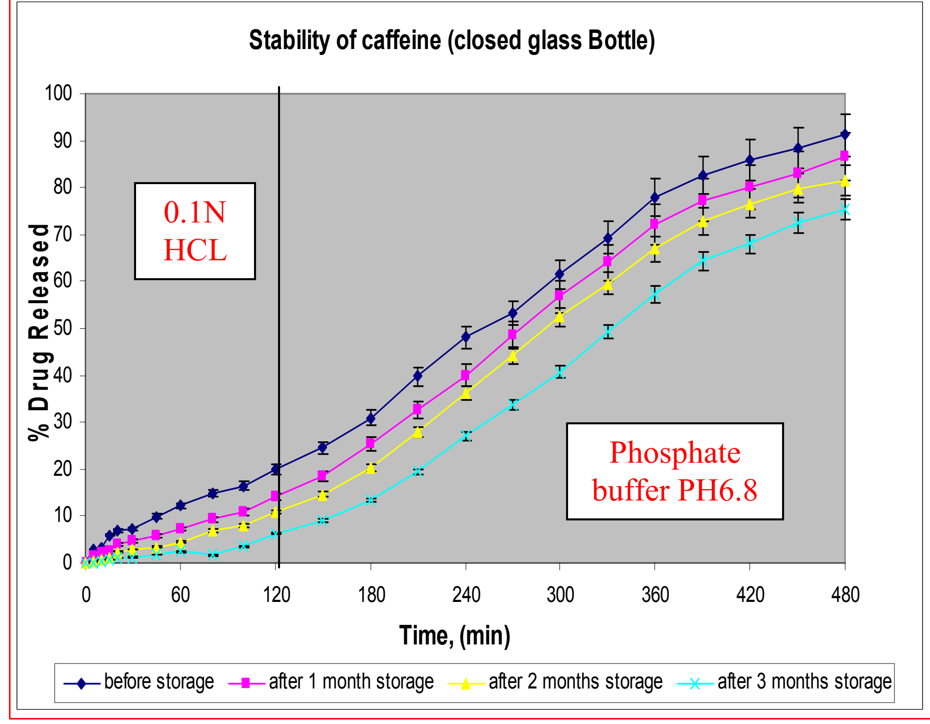


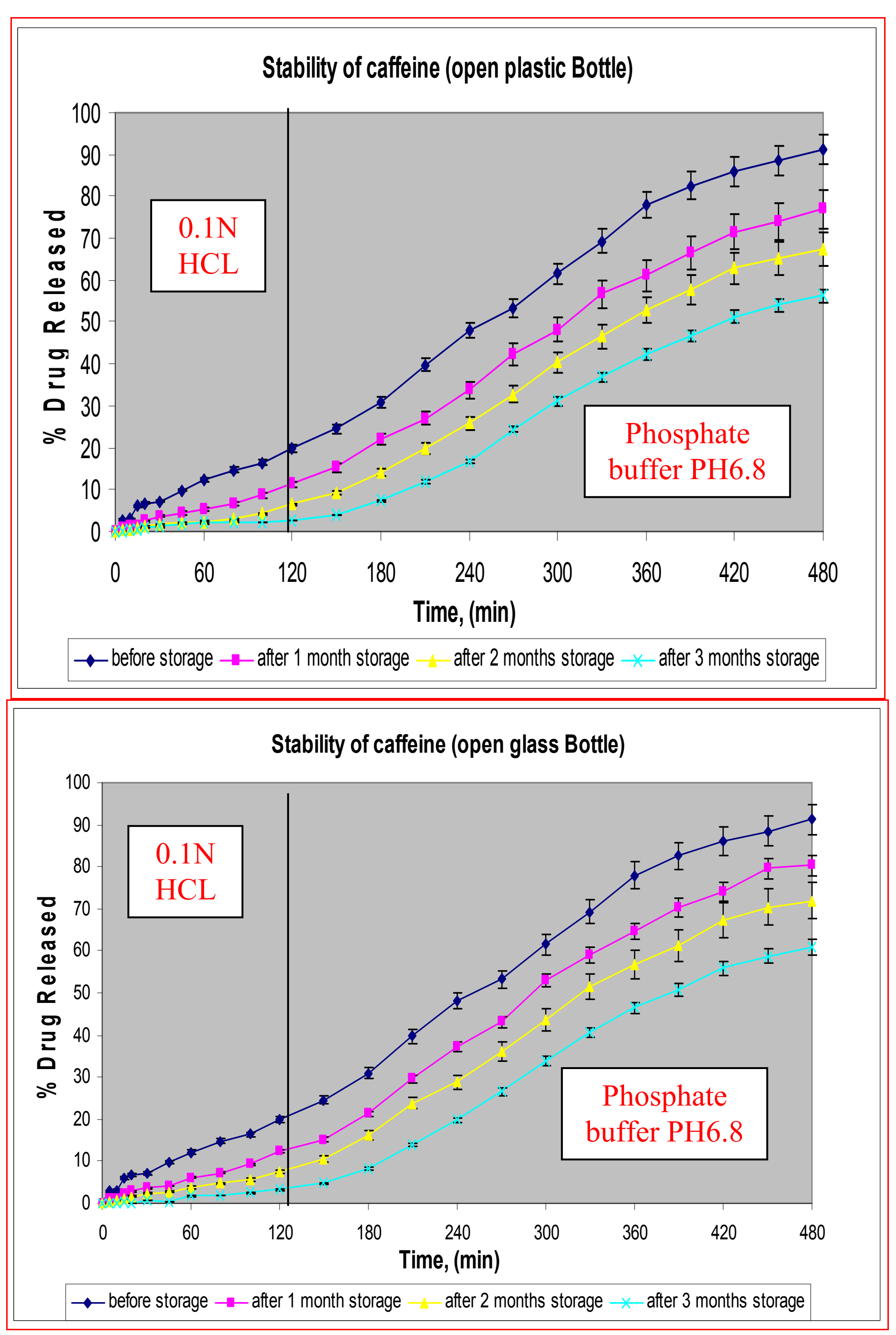
Figures 14. Release profiles of caffeine from multiparticulate beads stored At 40 DGC / 75% RH in different container after 3 months **Configuration (3)**

Configuration (4)




Stability of caffeine (closed plastic Bottle)
% Drug Released
0.1N HCL
Phosphate buffer PH6.8
Time ,(min)
before storage
before 1 month storage
after 2 months storage
after 3 months storage


Stability of caffeine (closed glass Bottle)
% Drug Released
0.1N HCL
Phosphate buffer PH6.8
Time, (min)
before storage
after 1 month storage
after 2 months storage
after 3 months storage



Figures 15. Release profiles of caffeine from multiparticulate beads stored at 40 DGC / 75% RH In different container after 3 months **Configuration (4)**

4.2.1. Interpretation of dissolution data in different pH mediums:-

The similarity factor (f2) is calculated from the dissolution data generated in different dissolution mediums at same speeds (50 rpm). The similarity factor is calculated between initial release profile and release profiles test in different pH mediums by following equation:-

$$F_2 = 50 \log [[1+ (1/n) \sum^{n}_{t=1} (R_r - T_t)^2]^{-0.5}]100]$$

Where n is the number of dissolution sampling times, and Rr and Tt are the individual or mean percent dissolved at each time point for the initial and test dissolution profiles respectively.

The similarity of the dissolution profiles was determined using the similarity factor (f2) three dissolution profiles are considered to be similar when the (f2) value is greater than 50 and dissimilar when less than 50, the (f2) values were found to be greater than 50 in 0.1N HCl at 50 rpm in all configurations (1, 2, 3,4) , in PH 4.5 Acetate buffer were found to be greater than 50 in all configurations (1, 2, 3, 4) and PH 6.8 were found to be greater than 50 in all configurations (1, 2, 3, 4) as shows in table (9) .Rate and extent of release of caffeine from the coated beads in different dissolution mediums were increased. Therefore, increase in f2 reflects on increase slightly in rate and extent of dissolution.

Table 9. In vitro Dissolution parameters of caffeine from pellet coated in three mediums

Sample. No , Configurations of multilayer coated beads	Dissolution Mediums	RPM	Similarity Factor (f2) between initial and release profiles test
1	0.1N HCl	50	52
	pH 4.5		60
	pH 6.8		72
2	0.1N HCl	50	69
	pH 4.5		85
	pH 6.8		91
3	0.1N HCl	50	72
	pH 4.5		85
	pH 6.8		100
4	0.1N HCl	50	53
	pH 4.5		56
	pH 6.8		69

Configuration (1)

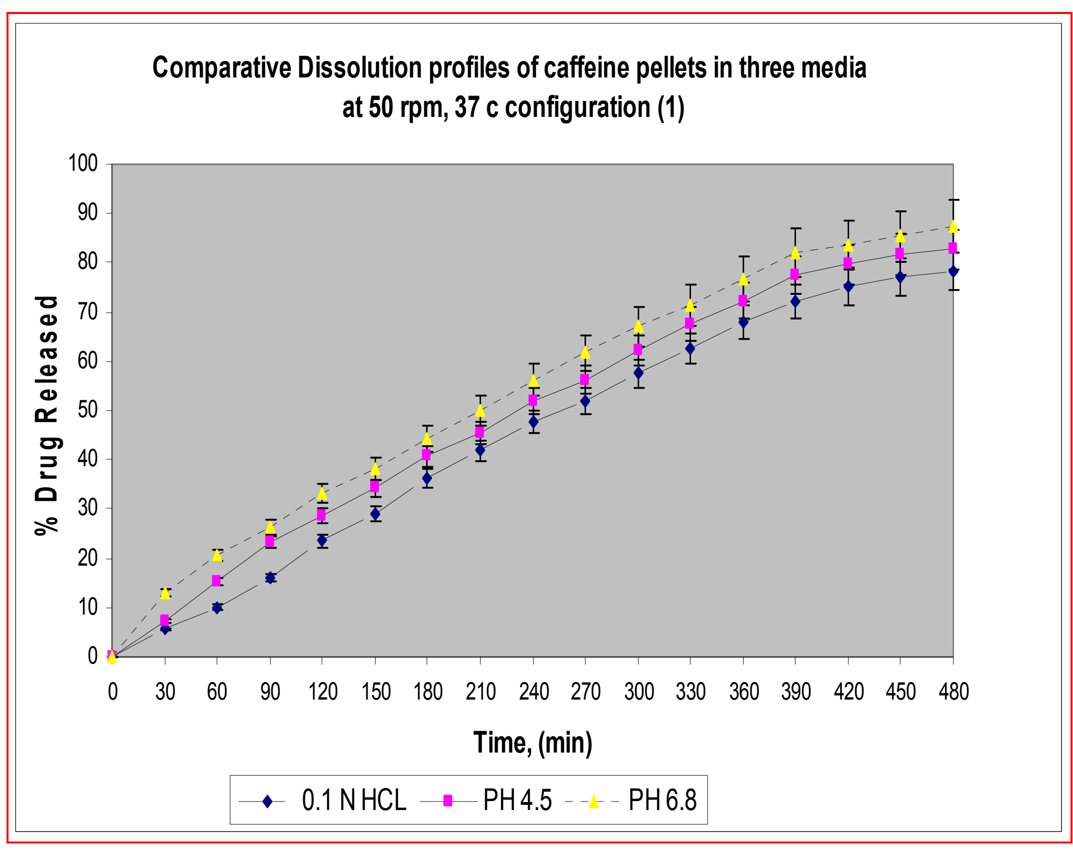
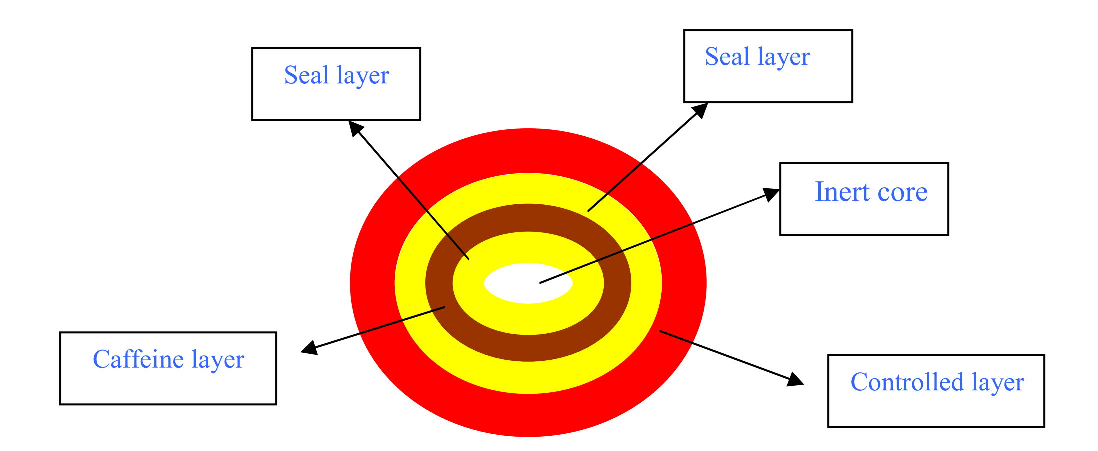


Figure 16. Comparative release profiles of caffeine Pellets in three media at 50 RPM, 37°C. **Configuration (1)**



Configuration (2)

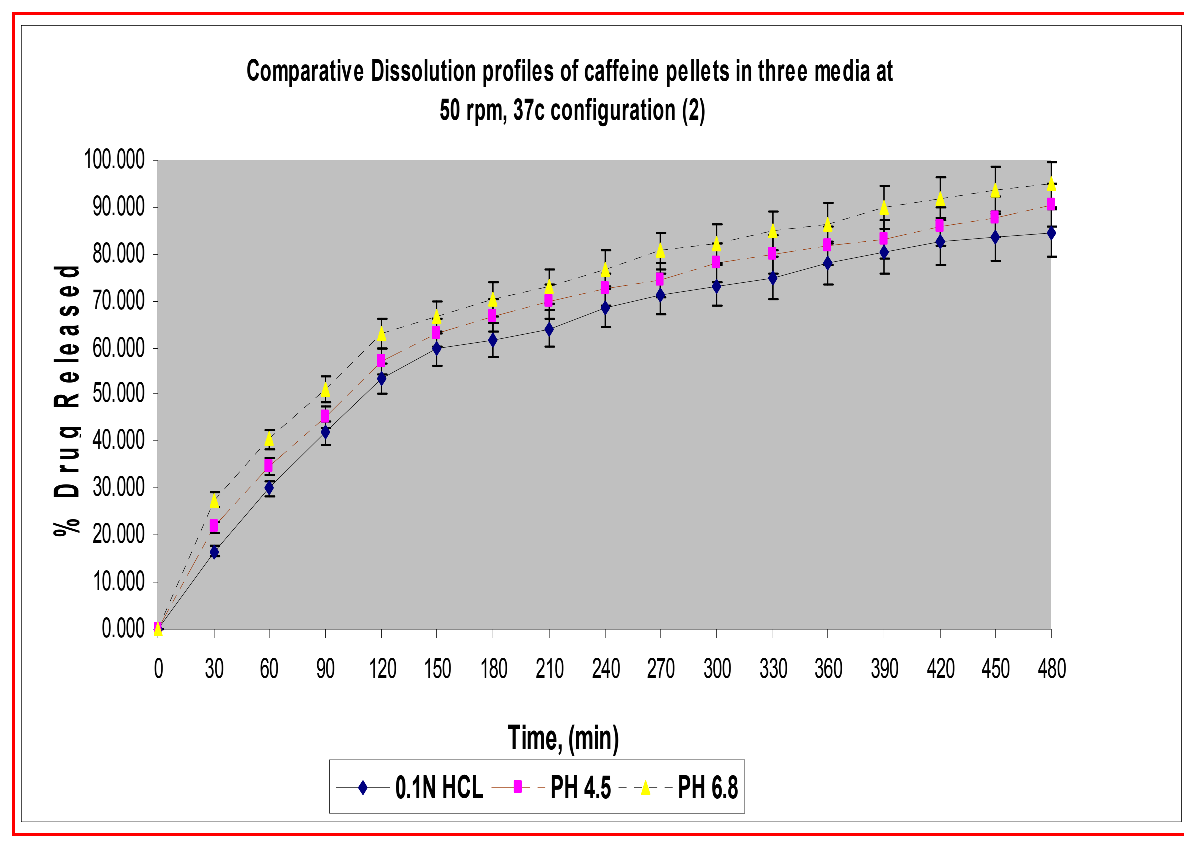
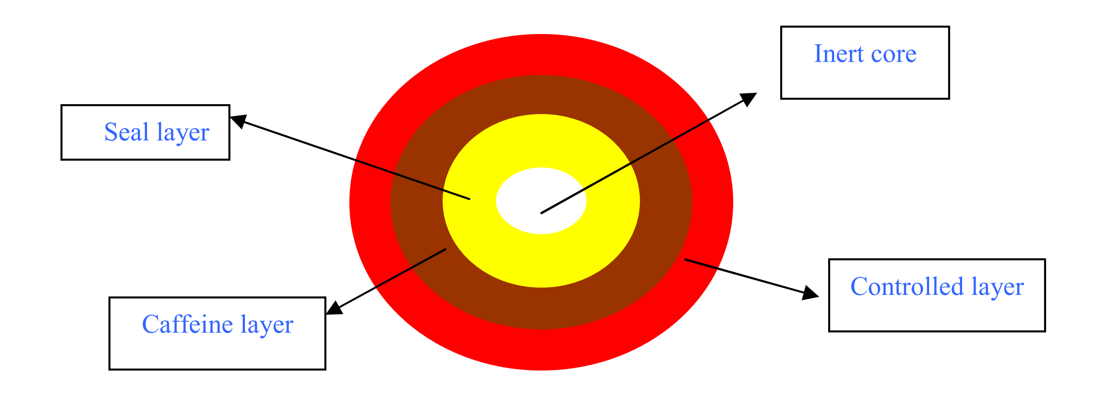


Figure 17. Comparative release profiles of caffeine Pellets in three media at 50 RPM 37°C **Configuration (2)**



Configuration (3)

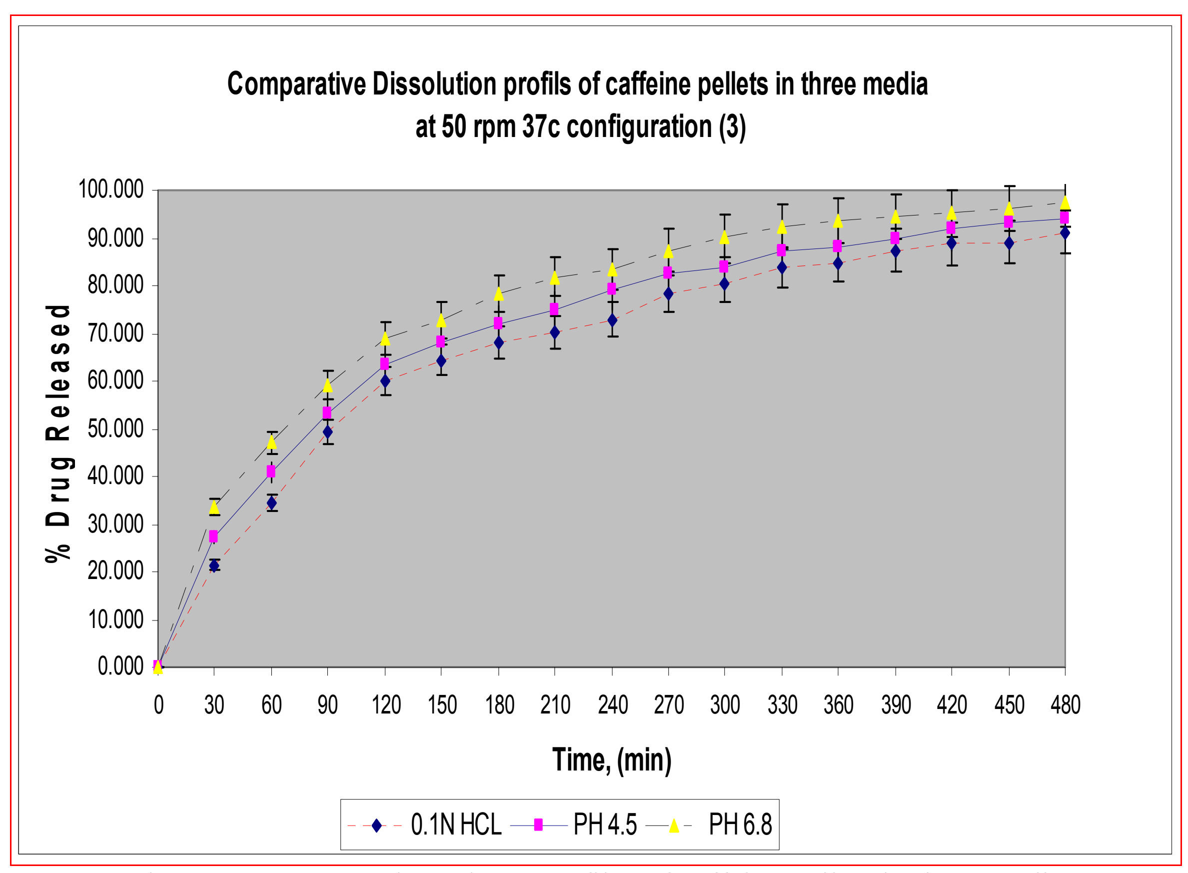
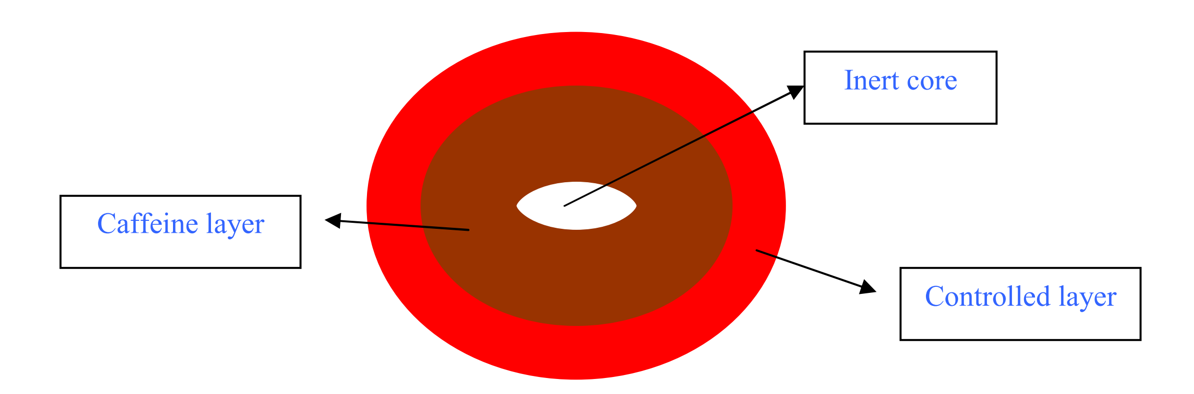


Figure 18. Comparative release profiles of caffeine pellets in three media at 50 RPM, 37°C. **Configuration (3)**



Configuration (4)

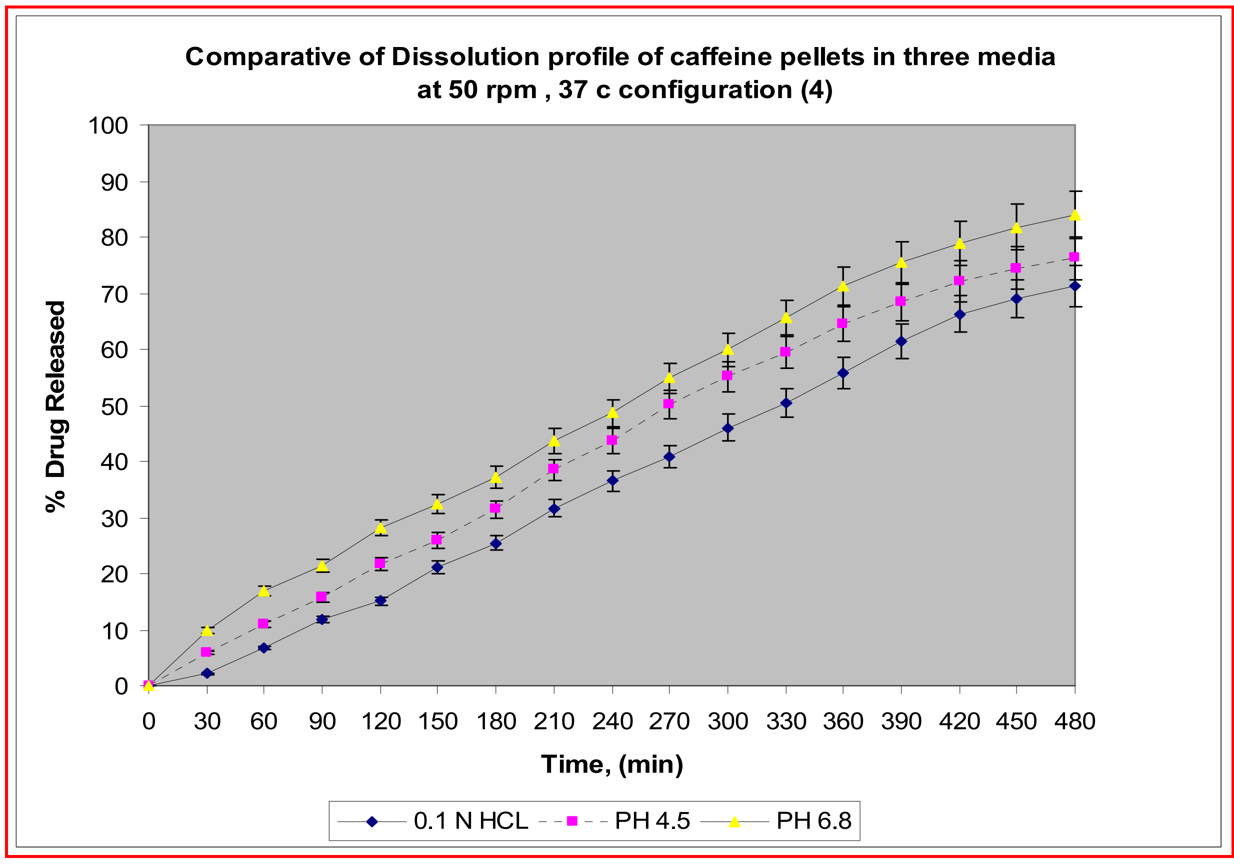
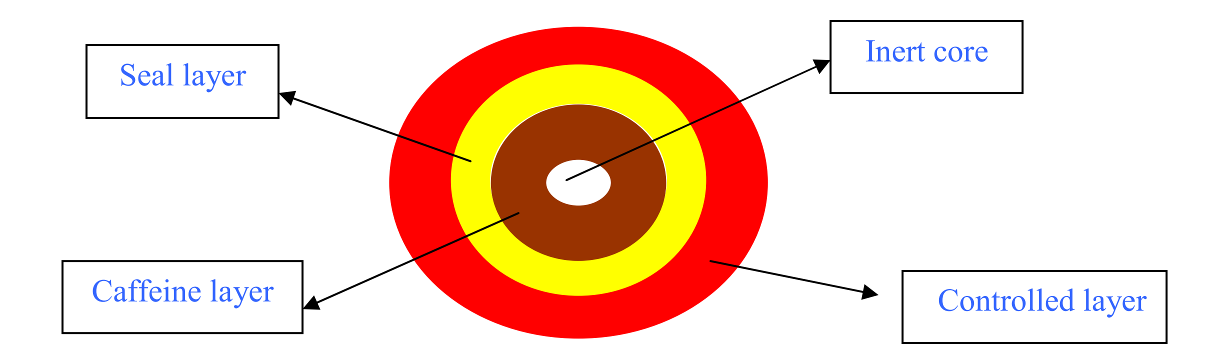


Figure 19. Comparative release profiles of caffeine pellets in three media at 50 RPM, 37°C. **Configuration (4)**



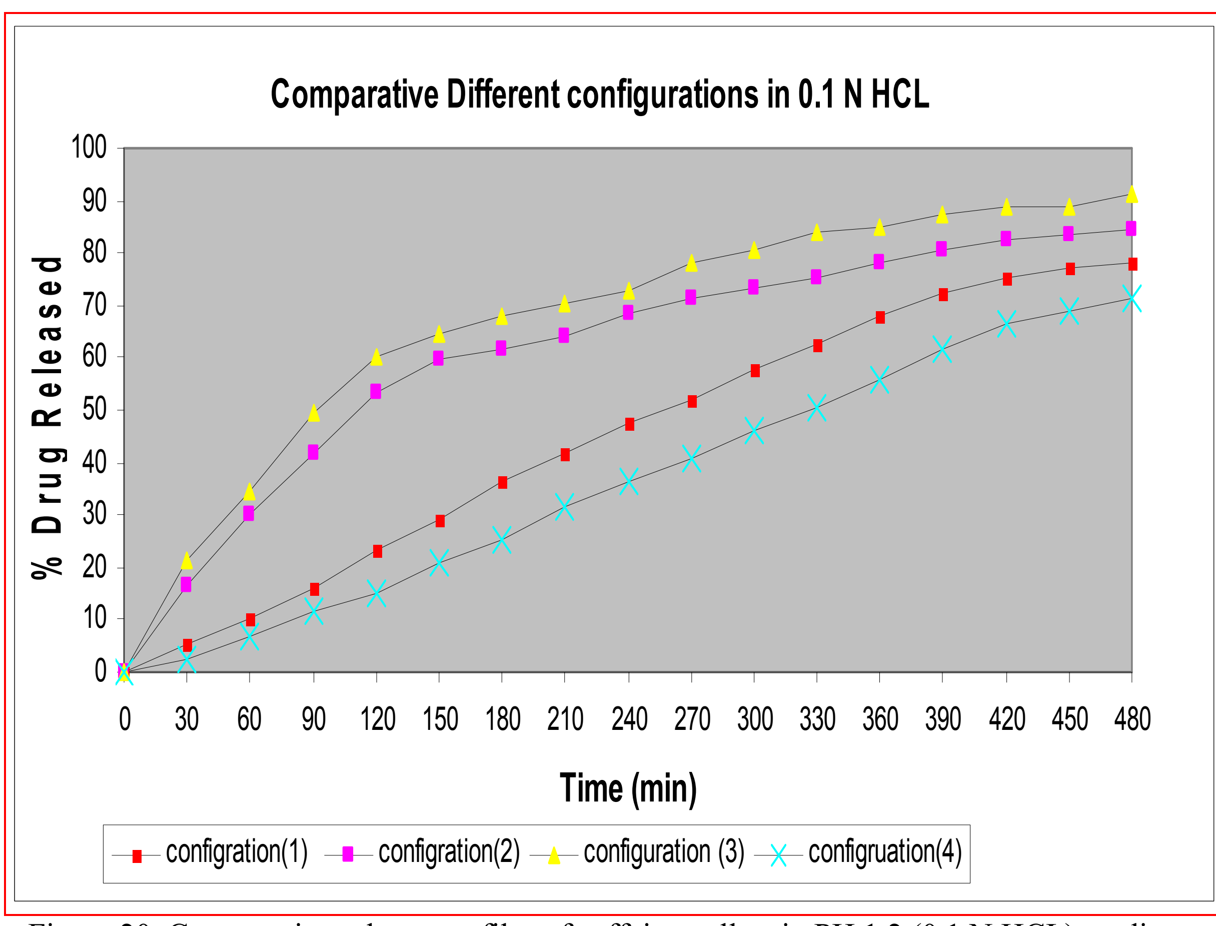


Figure 20. Comparative release profiles of caffeine pellets in PH 1.2 (0.1 N HCL) media at 50 RPM, 37°C in different configurations coated beads

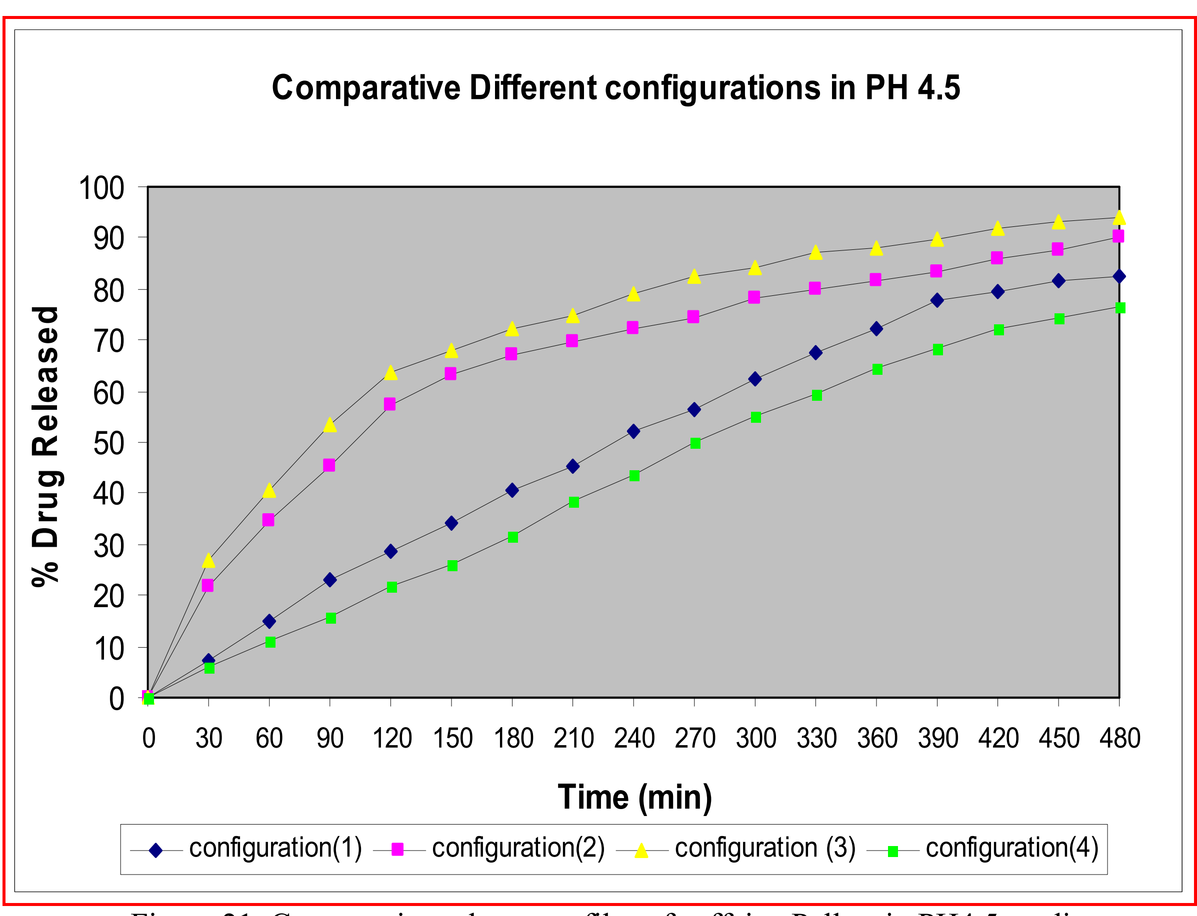


Figure 21. Comparative release profiles of caffeine Pellets in PH4.5 media at 50 RPM, 37°Cin different configurations coated beads

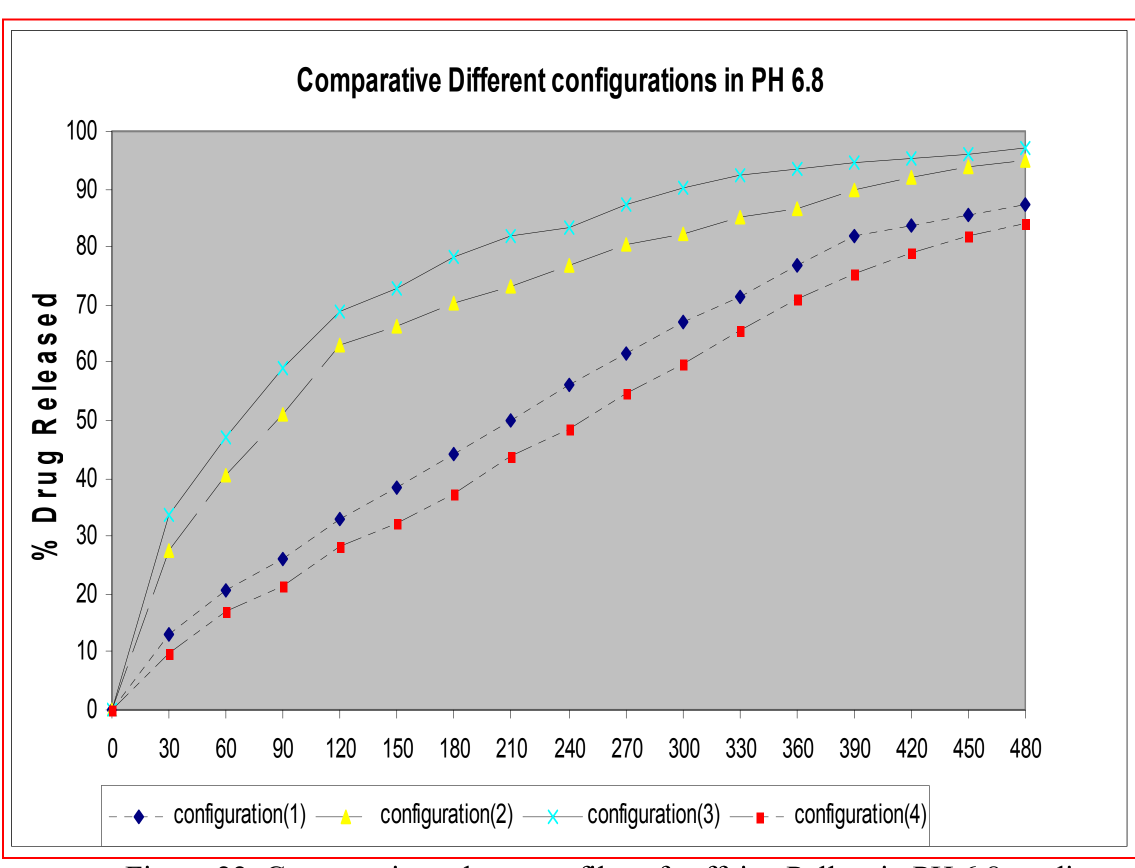


Figure 22. Comparative release profiles of caffeine Pellets in PH 6.8 media at 50 RPM, 37°C in different configurations coated beads

3. Effect of the Coating Levels of multilayer coated beads:-

3.1. Effect of the Coating Levels of seal layer on the drug release.

In order to improve the stability of the caffeine, the seal layer was coated on the drug-layered or starter core beads are shown release profile in figures (23, 26, 28, and 30). The seal layer did delay release of the caffeine from the drug-layered significant extent .As shown in figures (24,31), and the dissolution rate was almost the different from caffeine beads .Furthermore, variation in coating levels had influence on the dissolution profiles of caffeine . As shown in figure (33).

3.2. Effect of the Coating Levels of controlled layer on the drug release.

After coated with aqueous dispersion of methylacrylate copolymer **(**Eudragit RS, RL) which the coating level for controlled layer was different between four configurations were subsequently coated with different film thickness (weight gain). The rate of drug release was inversely proportional to the thickness of the coat, suggesting that the seal or controlled layer would increase the diffusion path length between the bead core and the dissolution medium. The rate of drug release from the one-layer film coated drug-layered beads was much faster than that from two-layer film coated drug-containing beads. When the seal or controlled film coating level was low the drug-layered beads released fast of caffeine whereas the drug-containing beads released slow when the seal or controlled film coating level was high .the release profiles of controlled caffeine layer bead coated. As shown in Figures (25, 26, 29, and 32).

Configuration (1)

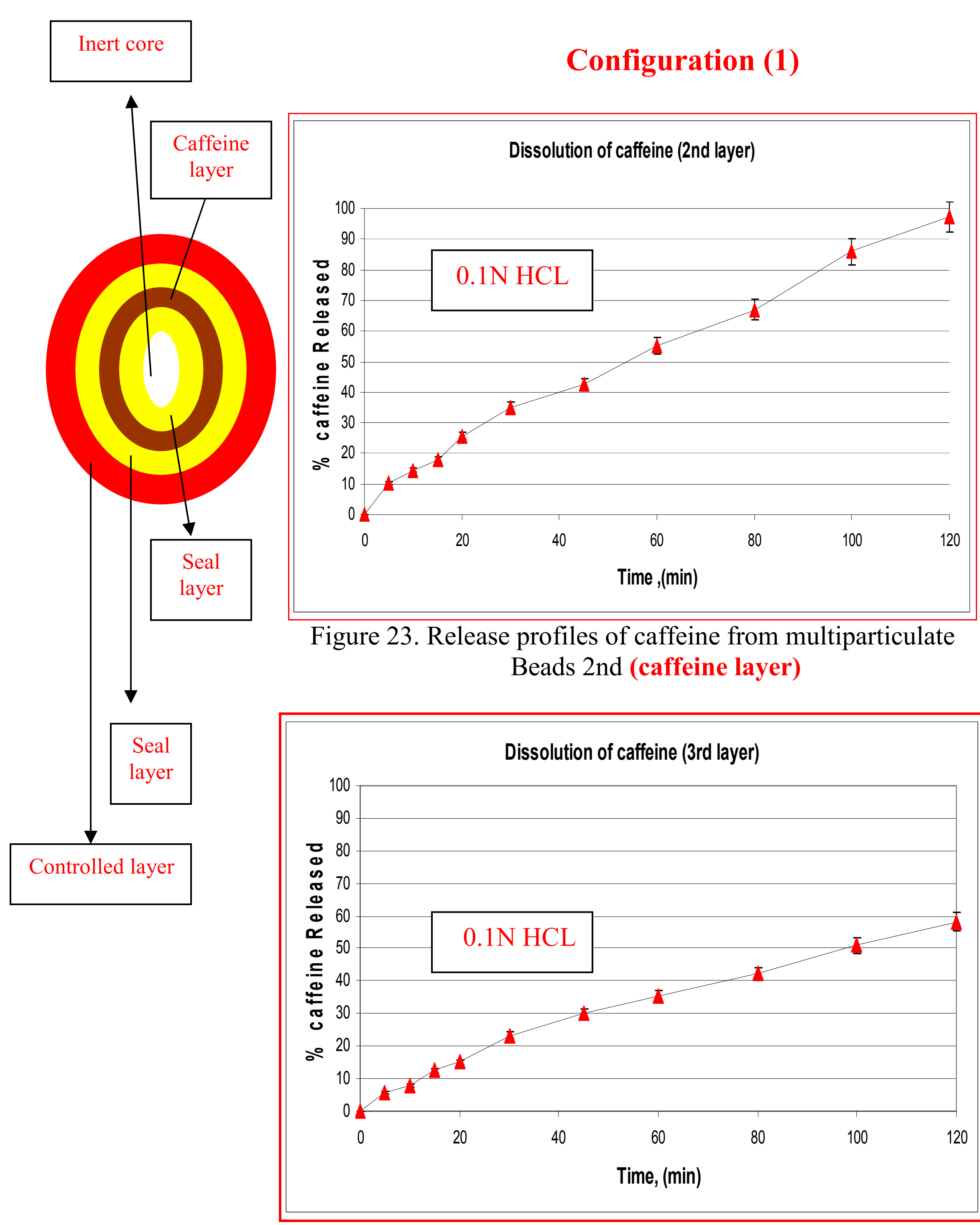


Figure 23. Release profiles of caffeine from multiparticulate Beads 2nd **(caffeine layer)**

Figure 24. Release profiles of caffeine from multiparticulate Beads 3rd **(seal layer)**

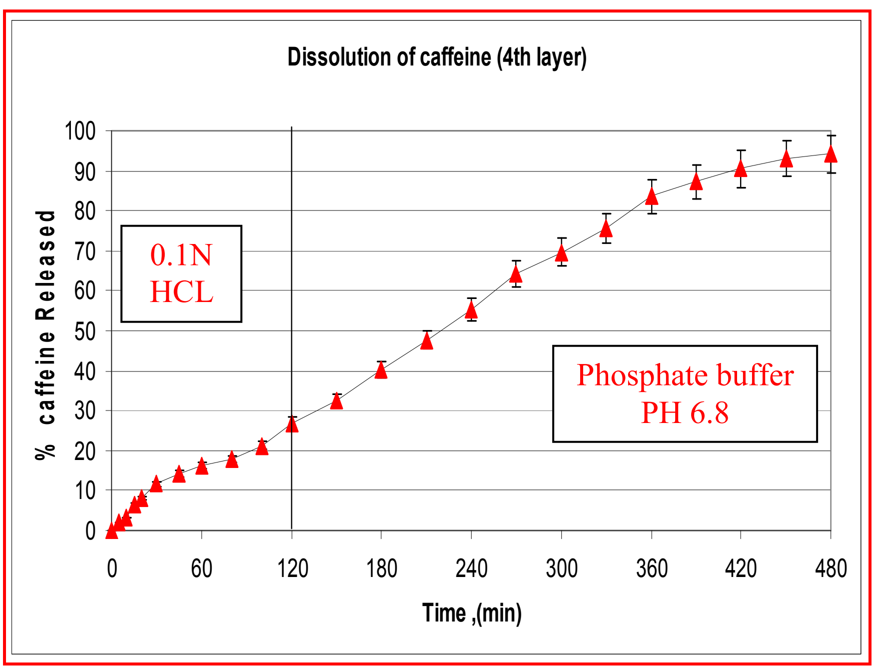


Figure 25. Release profiles of caffeine from multiparticulate Beads 4 th **(controlled layer)**

Configuration (2)

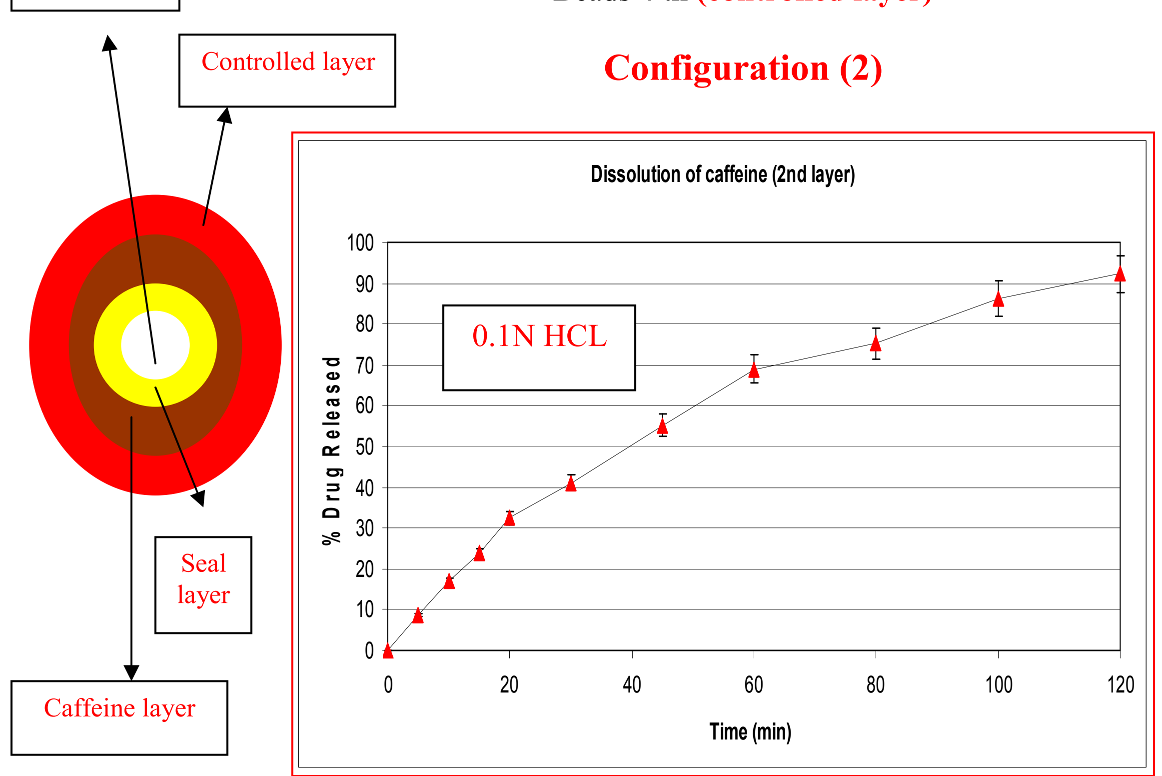


Figure 26. Release profiles of caffeine from multiparticulate Beads 2 nd **(caffeine layer)**

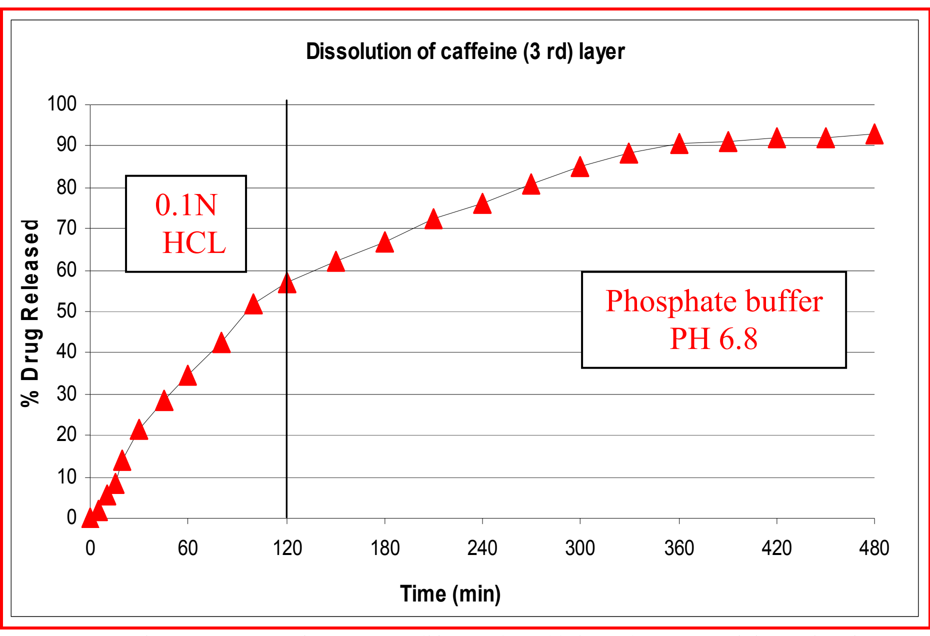


Figure 27. Release profiles of caffeine from multiparticulate Beads 3 rd **(controlled layer)**

Configuration (3)

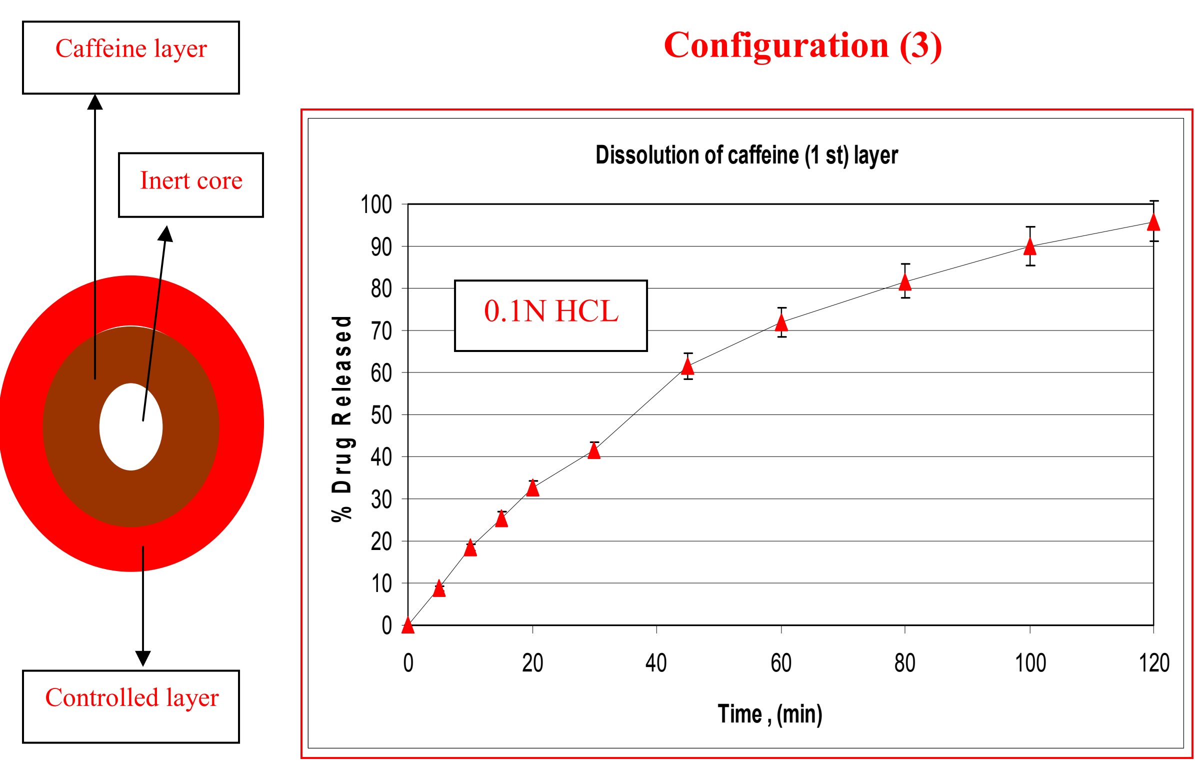


Figure 28. Release profiles of caffeine from multiparticulate Beads 1 st **(caffeine layer)**

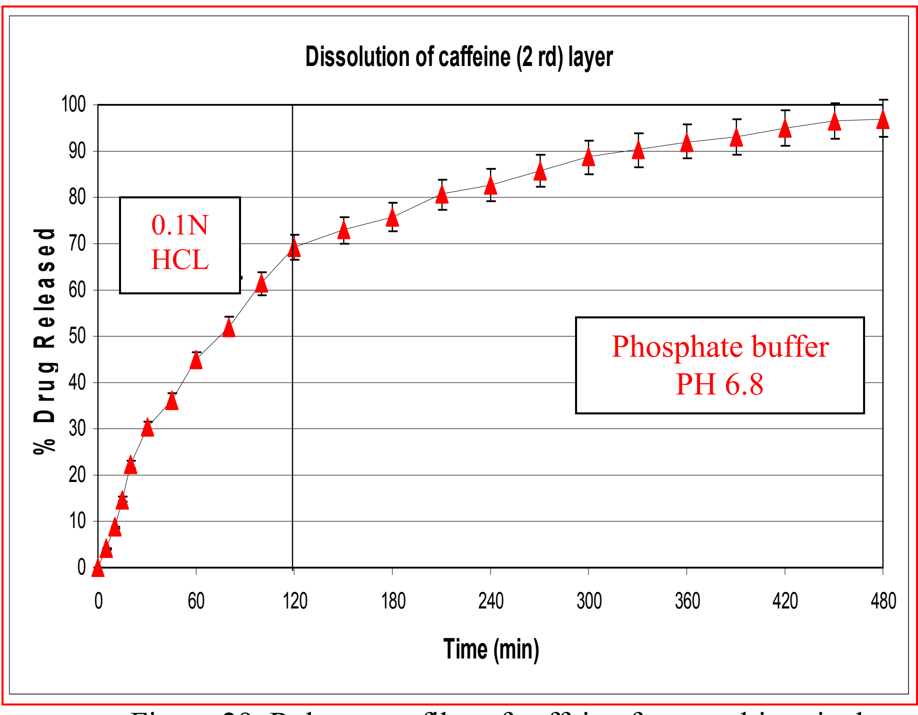


Figure 29. Release profiles of caffeine from multiparticulate Beads 2nd **(controlled layer)**

Configuration (4)

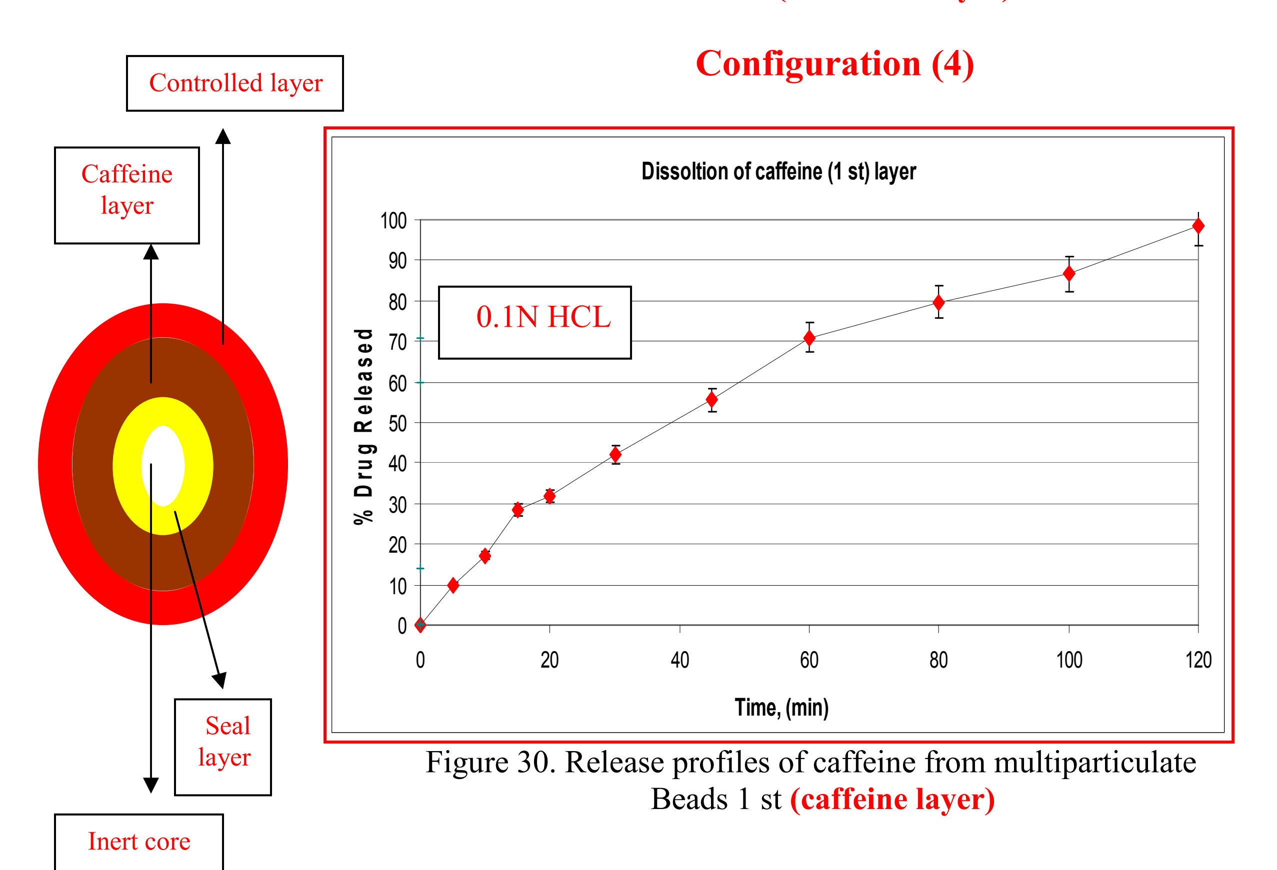


Figure 30. Release profiles of caffeine from multiparticulate Beads 1 st **(caffeine layer)**

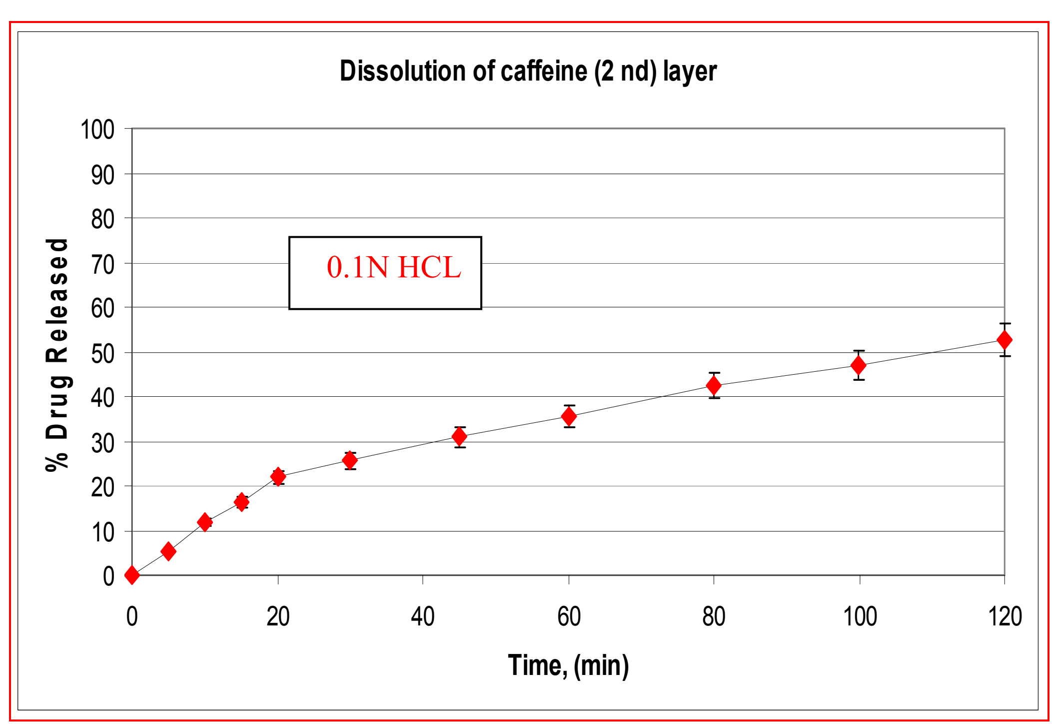


Figure 31. Release profiles of caffeine from multiparticulate Beads 2 nd **(seal layer)**

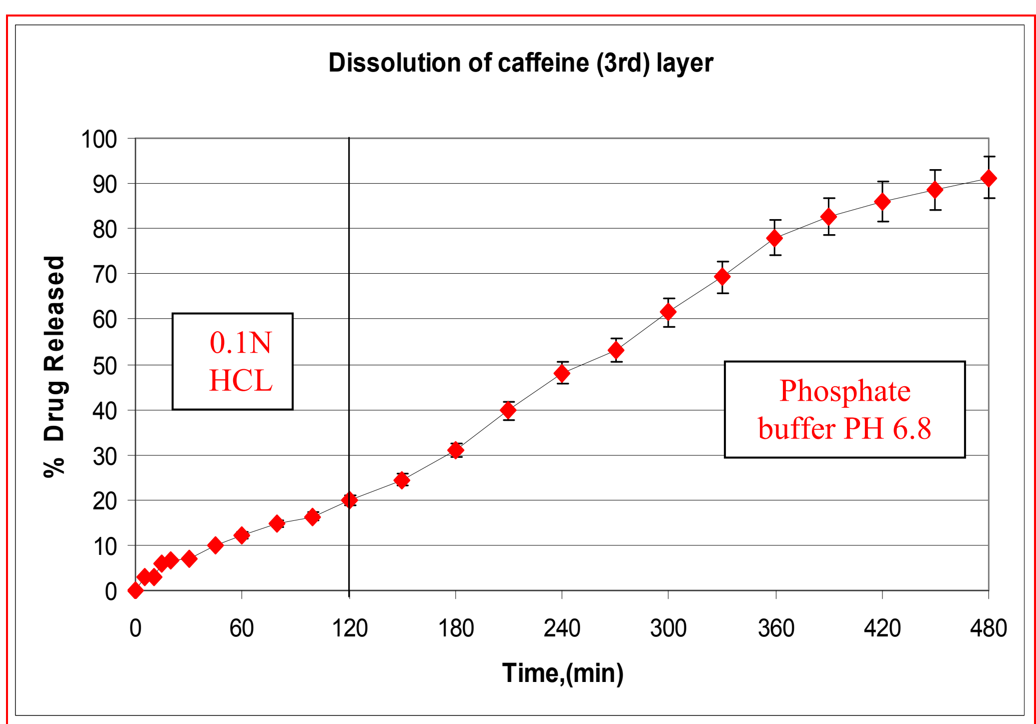


Figure 32. Release profiles of caffeine from multiparticulate Beads 3rd **(controlled layer)**

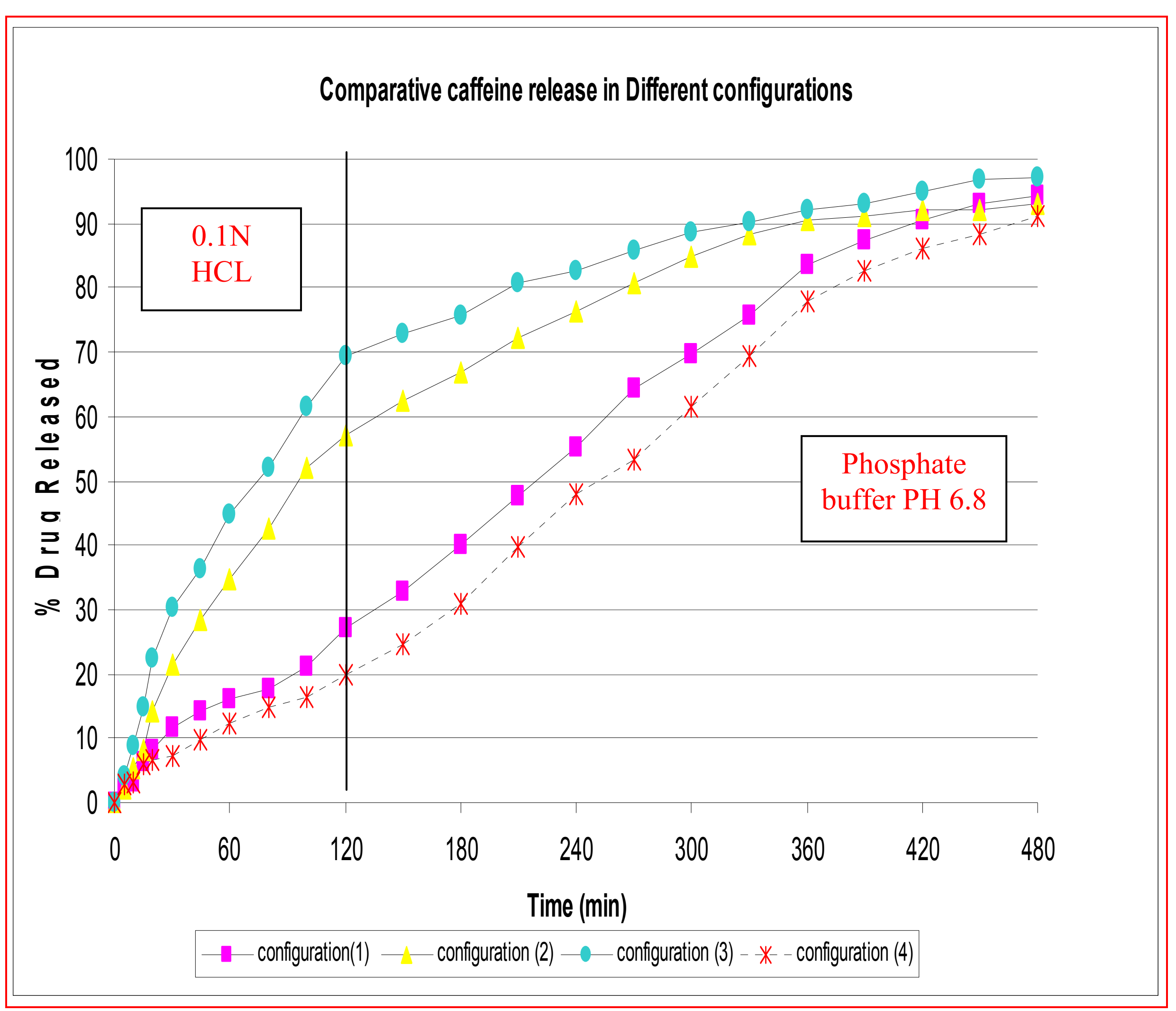


Figure33.Affects of the coating level (indicated in the diagrams) on drug release from methylacrylate RS, RL - copolymer 3:1 coated caffeine layered sugar cores in :(a) 0.1 N HCl (b) Phosphate buffer pH 6.8, at 50 RPM, 37°C in different configurations coating level

Configuration (1)

Table10. (**Configuration 1**) of multilayer caffeine pellet coated data

Seal layer	Drug layer	Seal layer	Controlled layer
Theoretical weight gain 547 grams	Theoretical weight gain 539.1 grams	Theoretical weight gain 518.5 grams	Theoretical weight gain 501.85 grams
Practical weight gain 542.3	Practical weight gain 530.7 grams	Practical weight gain 508.7 grams	Practical weight gain 491.7 gram
Weight loss 4.7 grams	Weight loss 8.4 grams	Weight loss 9.8 grams	Weight loss 10.15 grams
% yield 99.14	% Loading efficiency 88.38	% yield 98.1	% yield 97.98
Coating level 42.3 grams	% yield 98.44	Coating level 28 grams	Coating level 30 grams
% coating efficiency 90.00	Coating level 38.4 grams % coating efficiency 82.05	% coating efficiency 73.93	% coating efficiency 74.71

Configuration (2)

Table11. (**Configuration 3**) of multilayer caffeine pellet coated data

Drug layer	Controlled layer
Theoretical weight gain 552 grams	Theoretical weight gain 545.9 grams
Practical weight gain 544.6 grams	Practical weight gain 533.3 grams
Weight loss 7.4 grams	Weight loss 12.6 grams
% yield 98.65	% yield 97.7
% Loading efficiency 87.87	Coating level 38.7 grams
% coating efficiency 85.76 Coating level 44.6 grams	% coating efficiency 75.43

Configuration (3)

Table12. (**Configuration 3**) of multilayer caffeine pellet coated data

Drug layer		Seal layer	Controlled layer
Theoretical weight gain 552 grams		Theoretical weight gain 537.7 grams	Theoretical weight gain 525 grams
Practical weight gain 545.4 grams		Practical weight gain 529.4 grams	Practical weight gain 518.8 grams
Weight loss 6.6 grams		Weight loss 8.3 grams	Weight loss 6.2 grams
% Loading efficiency 91.87		% yield 98.46	% yield 98.82
% yield 98.8		Coating level 34 grams	Coating level 39.4 grams
Coating level 45.5 grams	% coating efficiency 87.3	% coating efficiency 80.37	% coating efficiency 86.4

Configuration (4)

Table13. (**Configuration 4**) of multilayer caffeine pellet coated data

Drug layer		Seal layer	Controlled layer
Theoretical weight gain 552 grams		Theoretical weight gain 537.7 grams	Theoretical weight gain 525 grams
Practical weight gain 545.4 grams		Practical weight gain 529.4 grams	Practical weight gain 518.8 grams
Weight loss 6.6 grams		Weight loss 8.3 grams	Weight loss 6.2 grams
% Loading efficiency 91.87		% yield 98.46	% yield 98.82
% yield 98.8		Coating level 34 grams	Coating level 39.4 grams
Coating level 45.5 grams	% coating efficiency 87.3	% coating efficiency 80.37	% coating efficiency 86.4

Appendixes of figures (8, 9, 10 and 11)
Configuration (1) Figure (8)
Dissolution of caffeine after (1 day)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.05233	0.60718711	0.00473
10	0.05833	2.84070632	0.00603
15	0.063	4.58971499	0.00954
20	0.071	7.58655514	0.00656
30	0.079	10.5982652	0.02427
45	0.08633	13.3770136	0.00289
60	0.09133	15.3019827	0.01137
80	0.094	16.3688352	0.00265
100	0.103	19.7950434	0.02088
120	0.11733	25.220632	0.02203
150	0.13367	31.4133209	0.01137
180	0.154	39.1122057	0.00721
210	0.17267	46.220632	0.01457
240	0.19333	54.0923792	0.03219
270	0.21533	62.4833333	0.00208
300	0.23033	68.2993185	0.00379
330	0.24667	74.6295539	0.02376
360	0.266	81.8166667	0.00624
390	0.27533	85.9702602	0.00802
420	0.28267	89.0167286	0.00603
450	0.28933	91.8023544	0.00321
480	0.2935	93.6406444	0.00071

Dissolution of caffeine after (1 week)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.05233	0.6071871	0.0047258
10	0.05667	2.2211276	0.0064291
15	0.06033	3.5952912	0.010116
20	0.064	4.9762701	0.001
30	0.06967	7.1075589	0.0138684
45	0.078	10.240706	0.005
60	0.08167	11.654523	0.0211266
80	0.08533	13.075155	0.0028868
100	0.09267	15.865675	0.0035119
120	0.10467	20.404647	0.0231157
150	0.12133	26.697708	0.0198578
180	0.14133	34.25285	0.0072342
210	0.15833	40.72311	0.0377403
240	0.17867	48.457311	0.0102144
270	0.19767	55.72311	0.0189033
300	0.20967	60.406506	0.0245832
330	0.22667	66.964126	0.010504
360	0.24167	72.540335	0.0030551
390	0.25133	76.751549	0.0140119
420	0.26533	82.250929	0.0092916
450	0.274	85.771375	0.005
480	0.281	88.657373	0.0098995

Dissolution of caffeine after (2 week)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.05133	0.2354399	0.00643
10	0.053	0.85619579	0.00458
15	0.05467	1.48004957	0.00902
20	0.058	2.72657993	0.00794
30	0.061	3.85539033	0.007
45	0.068	6.4767658	0.005
60	0.07333	8.49157373	0.0196
80	0.07567	9.40105328	0.00351
100	0.08233	11.9257745	0.00404
120	0.091	15.2063817	0.02152
150	0.107	21.2280669	0.01562
180	0.124	27.6481413	0.00889
210	0.13933	33.4771375	0.01124
240	0.15933	41.063259	0.01582
270	0.17433	46.8222429	0.00252
300	0.191	53.2156753	0.00361
330	0.20367	58.1431846	0.02577
360	0.218	63.4715613	0.02696
390	0.233	69.5966543	0.01153
420	0.24667	74.9572491	0.00635
450	0.25833	79.5836431	0.00666
480	0.264	82.2354994	0.00849

Dissolution of caffeine after (1 month)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.05233	0.60719	0.0073711
10	0.05267	0.73414	0.0056862
15	0.05267	0.73779	0.0011547
20	0.05433	1.36103	0.0061101
30	0.05433	1.36778	0.0032146
45	0.05867	2.98544	0.0050332
60	0.06233	4.36332	0.0064291
80	0.06533	5.50019	0.0066583
100	0.06867	6.76654	0.0081445
120	0.074	8.78259	0.0055678
150	0.08933	14.523	0.0208407
180	0.101	18.9282	0.0232594
210	0.115	24.2225	0.02
240	0.12967	29.7875	0.0049329
270	0.145	35.6277	0.0108167
300	0.16133	41.86	0.0086217
330	0.17567	47.3724	0.015308
360	0.194	54.1878	0.0500899
390	0.21	60.6072	0.048816
420	0.226	66.8178	0.0455082
450	0.23633	70.9418	0.0152753
480	0.24533	74.5607	0.0014142

Configuration (2) Figure (9)
Dissolution of caffeine after (1 day)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.0553333	1.7221341	0.007023769
10	0.0626667	4.45718711	0.01474223
15	0.0696667	7.08166047	0.005859465
20	0.0816667	11.577881	0.014153916
30	0.0976667	17.5833953	0.013316656
45	0.1196667	25.8491326	0.017559423
60	0.1356667	31.9252788	0.009073772
80	0.158	40.3855638	0.009539392
100	0.1803333	48.8873606	0.01274101
120	0.198	55.6958488	0.006082763
150	0.2103333	60.5459108	0.01274101
180	0.2206667	64.661772	0.009073772
210	0.2343333	70.0229864	0.010503968
240	0.2433333	73.6524783	0.009291573
270	0.256	78.6320322	0.011789826
300	0.2673333	83.098575	0.005859465
330	0.2726667	85.3259603	0.004041452
360	0.28	88.0521066	0.009643651
390	0.2823333	89.55886	0.006110101
420	0.2843333	90.6524164	0.007505553
450	0.2843333	90.6524164	0.007505553
480	0.286	91.4095415	0.008888194

Dissolution of caffeine after (1 week)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.055666667	1.84634449	0.0125033
10	0.059	3.09473358	0.0051962
15	0.066333333	5.83630731	0.0025166
20	0.076	9.45892193	0.03005
30	0.091333333	15.2060719	0.0266333
45	0.106333333	20.858767	0.0170098
60	0.128	29.0157373	0.004
80	0.146	35.8508674	0.0091652
100	0.163666667	42.595539	0.0166533
120	0.183	49.992627	0.004
150	0.199333333	56.3011772	0.0109697
180	0.209666667	60.4034077	0.0020817
210	0.218666667	64.0155514	0.0020817
240	0.228333333	67.8742875	0.0102632
270	0.238333333	71.8464064	0.0136137
300	0.245666667	74.8179058	0.0233524
330	0.252333333	77.5149318	0.0210317
360	0.255	78.5062577	0.0157162
390	0.257	79.8271375	0.0072111
420	0.259333333	80.8680297	0.0057735
450	0.262333333	82.1251549	0.0192959
480	0.262666667	82.366171	0.0115902

Dissolution of caffeine after (2 week)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.0526667	0.73110285	0.009073772
10	0.0546667	1.47825279	0.001527525
15	0.06	3.46827757	0.003605551
20	0.067	6.0877943	0.009539392
30	0.0806667	11.1986369	0.00321455
45	0.097	17.3262082	0.02116601
60	0.1173333	24.9711276	0.008962886
80	0.1323333	30.6711896	0.009073772
100	0.1506667	37.63829	0.006658328
120	0.165	43.1524783	0.008185353
150	0.1826667	49.9288104	0.008386497
180	0.1943333	54.5037794	0.03442867
210	0.2036667	58.2231103	0.017214335
240	0.2106667	61.079368	0.019087518
270	0.2183333	64.1710657	0.029280255
300	0.2246667	66.7509913	0.034122329
330	0.2293333	68.685316	0.036143234
360	0.2343333	70.544052	0.002516611
390	0.237	72.0570012	0.009539392
420	0.2403333	73.4566295	0.014189198
450	0.242	74.216233	0.013747727
480	0.245	75.4417596	0.007211103

Dissolution of caffeine after (1 month)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.051666667	0.35935564	0.0090738
10	0.053666667	1.10464684	0.0090185
15	0.055	1.60582404	0.0104403
20	0.058666667	2.97688971	0.0140119
30	0.066666667	5.96567534	0.0092916
45	0.086666667	13.4302974	0.0077675
60	0.1	18.4537794	0.0212838
80	0.119666667	25.8564436	0.0032146
100	0.132333333	30.6934325	0.0105987
120	0.148	36.6692069	0.0087178
150	0.161666667	41.9288104	0.0070946
180	0.174	46.7144362	0.0072111
210	0.180666667	49.4139405	0.0075719
240	0.185333333	51.3755266	0.0202073
270	0.192	54.0744114	0.0367151
300	0.195666667	55.6332714	0.0345881
330	0.2	57.421995	0.0275136
360	0.201666667	58.0415737	0.0174738
390	0.203666667	59.2149938	0.0095044
420	0.205	59.8432466	0.0339559
450	0.208	61.0644362	0.0345109
480	0.210333333	62.0179678	0.0362951

Configuration (3) Figure (10)
Dissolution of caffeine after (1 day)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.06	3.4572491	0.01253
10	0.067	6.0767658	0.012
15	0.084	12.426766	0.006928
20	0.1006667	18.684449	0.01097
30	0.1203333	26.088352	0.002082
45	0.1396667	33.404895	0.024111
60	0.1626667	42.120446	0.01365
80	0.1823333	49.639591	0.015535
100	0.2053333	58.434449	0.032655
120	0.225	66.0329	0.00755
150	0.2336667	69.5614	0.009504
180	0.2423333	73.092999	0.013013
210	0.2533333	77.476518	0.002517
240	0.2583333	79.619021	0.01914
270	0.266	82.725589	0.007
300	0.272	85.190892	0.009539
330	0.2806667	88.615923	0.010214
360	0.2846667	90.102912	0.007638
390	0.2873333	91.711896	0.006028
420	0.2913333	93.351301	0.006658
450	0.2933333	94.218092	0.010504
480	0.296	95.320322	0.001414

Dissolution of caffeine after (1 week)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.057	2.3420074	0.00556776
10	0.064	4.955948	0.0072111
15	0.078	10.18513	0.011
20	0.0883333	14.077261	0.01209683
30	0.1043333	20.095167	0.01422439
45	0.1266667	28.497212	0.00057735
60	0.142	34.338538	0.01053565
80	0.1623333	42.0671	0.01274101
100	0.1833333	50.081289	0.00550757
120	0.1926667	53.79746	0.01361372
150	0.2053333	58.758426	0.0595007
180	0.217	63.358178	0.006
210	0.2253333	66.714436	0.02557994
240	0.2316667	69.323482	0.01006645
270	0.2396667	72.534139	0.01724336
300	0.244	74.355081	0.02151743
330	0.2483333	76.155576	0.00665833
360	0.254	78.262144	0.01212436
390	0.2573333	80.039033	0.02804164
420	0.26	81.167906	0.0153948
450	0.2633333	82.532218	0.01680278
480	0.2656667	83.507435	0.00636396

Dissolution of caffeine after (2 week)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.0536667	1.1028501	0.001528
10	0.056	1.9757745	0.003464
15	0.0636667	4.8356877	0.010408
20	0.072	7.9576828	0.005
30	0.088	13.945229	0.00755
45	0.1033333	19.714684	0.028113
60	0.1196667	25.884387	0.013279
80	0.1413333	34.0671	0.018148
100	0.159	40.803098	0.016371
120	0.174	46.580607	0.018248
150	0.188	52.008736	0.039837
180	0.197	55.599814	0.031432
210	0.2033333	58.202045	0.024111
240	0.2093333	60.676642	0.040796
270	0.215	63.008736	0.052374
300	0.219	64.703284	0.051468
330	0.2236667	66.622739	0.037581
360	0.228	68.233643	0.054525
390	0.2306667	69.707559	0.003512
420	0.2333333	70.832094	0.017786
450	0.2343333	71.314126	0.01097
480	0.2383333	72.887237	0.028284

Dissolution of caffeine after (1 month)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.0516667	0.3593556	0.0005774
10	0.0526667	0.7328996	0.0056862
15	0.0583333	2.8431227	0.0118462
20	0.0613333	3.9725527	0.0050332
30	0.0706667	7.4619579	0.0040415
45	0.082	11.712206	0.0130767
60	0.103	19.577076	0.0164621
80	0.117	24.878748	0.0202978
100	0.135	31.693432	0.0112694
120	0.1466667	36.187175	0.0120968
150	0.155	39.461648	0.03005
180	0.165	43.369331	0.011
210	0.1716667	46.045911	0.0134288
240	0.1753333	47.614064	0.0292973
270	0.1776667	48.676022	0.0346458
300	0.1853333	51.703903	0.0454569
330	0.1866667	52.352602	0.0345012
360	0.1883333	52.972181	0.0406489
390	0.19	53.977076	0.0131149
420	0.193	55.194548	0.0163707
450	0.1983333	57.263321	0.0225906
480	0.1996667	57.839529	0.0077782

Configuration (4) Figure (11)
Dissolution of caffeine after (1 day)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.06	3.457291	0.01253
10	0.067	6.0767658	0.012
15	0.084	12.426766	0.006928
20	0.1006667	18.684449	0.01097
30	0.1203333	26.088352	0.002082
45	0.1396667	33.404895	0.024111
60	0.1626667	42.120446	0.01365
80	0.1823333	49.639591	0.015535
100	0.2053333	58.434449	0.032655
120	0.225	66.0329	0.00755
150	0.2336667	69.5614	0.009504
180	0.2423333	73.092999	0.013013
210	0.2533333	77.476518	0.002517
240	0.2583333	79.619021	0.01914
270	0.266	82.725589	0.007
300	0.272	85.190892	0.009539
330	0.2806667	88.615923	0.010214
360	0.2846667	90.102912	0.07638
390	0.2873333	91.711896	0.006028
420	0.2913333	93.351301	0.006658
450	0.2933333	94.218092	0.010504
480	0.296	95.320322	0.001414

Dissolution of caffeine after (1 week)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.057	2.3420074	0.00556776
10	0.064	4.955948	0.0072111
15	0.078	10.18513	0.011
20	0.0883333	14.077261	0.01209683
30	0.1043333	20.095167	0.01422439
45	0.1266667	28.497212	0.00057735
60	0.142	34.338538	0.01053565
80	0.1623333	42.0671	0.01274101
100	0.1833333	50.081289	0.00550757
120	0.1926667	53.79746	0.01361372
150	0.2053333	58.758426	0.0595007
180	0.217	63.358178	0.006
210	0.2253333	66.714436	0.02557994
240	0.2316667	69.323482	0.01006645
270	0.2396667	72.534139	0.01724336
300	0.244	74.355081	0.02151743
330	0.2483333	76.155576	0.00665833
360	0.254	78.262144	0.01212436
390	0.2573333	80.039033	0.02804164
420	0.26	81.167906	0.0153948
450	0.2633333	82.532218	0.01680278
480	0.2656667	83.507435	0.00636396

Dissolution of caffeine after (2 week)

Time (min	Average (ABS)	% Release	S.D
0	0	0	0
5	0.0536667	1.1028501	0.001528
10	0.056	1.9757745	0.003464
15	0.0636667	4.8356877	0.010408
20	0.072	7.9576828	0.005
30	0.088	13.945229	0.00755
45	0.1033333	19.714684	0.028113
60	0.1196667	25.884387	0.013279
80	0.1413333	34.0671	0.018148
100	0.159	40.803098	0.016371
120	0.174	46.580607	0.018248
150	0.188	52.008736	0.039837
180	0.197	55.599814	0.031432
210	0.2033333	58.202045	0.024111
240	0.2093333	60.676642	0.040796
270	0.215	63.008736	0.052374
300	0.219	64.703284	0.051468
330	0.2236667	66.622739	0.037581
360	0.228	68.233643	0.054525
390	0.2306667	69.707559	0.003512
420	0.2333333	70.832094	0.017786
450	0.2343333	71.314126	0.01097
480	0.2383333	72.887237	0.028284

Dissolution of caffeine after (1month)

Time (min)	Average (ABS)	% Release	S.D
0	0	0	0
5	0.0516667	0.3593556	0.0005774
10	0.0526667	0.7328996	0.0056862
15	0.0583333	2.8431227	0.0118462
20	0.0613333	3.9725527	0.0050332
30	0.0706667	7.4619579	0.0040415
45	0.082	11.712206	0.0130767
60	0.103	19.577076	0.0164621
80	0.117	24.878748	0.0202978
100	0.135	31.693432	0.0112694
120	0.1466667	36.187175	0.0120968
150	0.155	39.461648	0.03005
180	0.165	43.369331	0.011
210	0.1716667	46.045911	0.0134288
240	0.1753333	47.614064	0.0292973
270	0.1776667	48.676022	0.0346458
300	0.1853333	51.703903	0.0454569
330	0.1866667	52.352602	0.0345012
360	0.1883333	52.972181	0.0406489
390	0.19	53.977076	0.0131149
420	0.193	55.194548	0.0163707
450	0.1983333	57.263321	0.0225906
480	0.1996667	57.839529	0.0077782

CONCLUSIONS

The following conclusions can be drawn from the study. Multi unit particulate system has long been employed to improve the bioavailability of drugs. Several factors were studied such as thickness coating and duration of accelerated stability and curing conditions as responsible factors for the cumulative amount of caffeine released for 8 hour from coated beads.

In conclusion, an increase in coating weight gain (thickness coating) decreased the rate and extent of release of caffeine from coated beads simply because of the increased permeability and distance across the membrane. And also the release profile of caffeine from coated beads found to be decrease in rate and extent was observed from coated beads stored at 50 °C in an oven as well as under stress conditions at (40 °C and 75 % RH), Drug release was significantly affected by the configuration of the system and zero order drug release was achieved with some configurations.

Finally, multiparticulate drug delivery systems provide huge opportunities for designing new controlled and delayed release oral formulations.

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APPENDICES

- **Drug release data and Drug content data of different configurations multilayer caffeine pellet coated formulations.**
- **Drug release data of pellet coated after storage under curing conditions.**
- **Drug release data of of pellet coated before and after storage under accelerated stability conditions.**
- **Drug release data, and Drug content data of different configurations multilayer caffeine pellet coated formulations**
- **Drug release data of pellet coated in different PH medium according FDA recommendation**

تأثير مجموعة أنظمة إيصال الدواء على أداء حبوب متعددة الطبقات

أعداد
فراس فالح المعموري

المشرف
الدكتور.حاتم الخطيب

المشرف المشارك
الدكتور.نبيل دروزة

ملخـــــص

الغرض من هذه الدراسة هو تطوير وأعداد حبيبات الكافيين طويل المفعول المعدة بواسطة تقنية التحبب.
التحكم في تحرر حبيبات الكافيين يحضر عن طريق تحميل الكافيين على حبات خاملة تليها طبقات خارجية من أطلية مختلفة البوليمرية الوظيفية بواسطة مخاليط مائية التشتت مثل Eudragit® E_{100} استخدمت كطلاء واقي و أطلية من مختلف خصائص الذوبان يمكن أن تنتج من أ مينو ميثاكريليت كوبوليمر (Eudragit RL 30 D) وأ مينو ميثاكريليت كوبوليمر (Eudragit RS 30 D) استخدمت كطلية لتحرير الدواء طويل المفعول المستخدمة بنسبة 70:30 بواسطة جهاز السائل السرير المغطى (عمود فور ستر).
سمك الطلاء ، ومدة علاج الحراري أو تسارع حالة الاستقرار وظروف العملية المستخدمة مثل درجة الحرارة ، وتدفق الهواء يؤثر على التحرر الكافيين من الخرز المغلفة خلال 8 ساعات.
تعرض حبيبات الكافيين المغلفة للانحلال في (0.1 ن) هيدروكلورايد لمدة 2 ساعة (والرقم الهيدروجيني 6.8) لمدة 6 ساعات، للتقييم تحرير الدواء من الخرز المحببة وتم تخزين حبيبات الكافيين في الفرن على درجة حرارة 50 درجة مئوية وتسارعت حالة الاستقرار على 40 درجة مئوية ورطوبة نسبية 75% في جميع الحالات كان معدل تحرر الكافيين من الخرز المغلفة المخزنة تنخفض من الخرز المغلفة.

وفي الختام، تكنولوجيا التحبب قد أحدثت ثورة في البحوث الدوائية مع مجموعة واسعة من التطبيقات التي تشمل تحرر الأدوية الفورية وطويلة المفعول، بالحقن عن طريق الفم، والمنتجات تحت الجلد.